PATENT COOPERATION TF ATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 06 April 2000 (06.04.00)	
International application No.: PCT/JP99/05224	Applicant's or agent's file reference: 99298M
International filing date: 24 September 1999 (24.09.99)	Priority date: 25 September 1998 (25.09.98)
Applicant: WATANABE, Kazutoshi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

07 February 2000 (07.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D409/14 C07D401/14 A61K31/506

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application page 172 -page 230; examples 4-8,24,29,33; table 1 ---	1,6,8-12
X	EP 0 168 262 A (FUJISAWA) 15 January 1986 (1986-01-15) page 40 -page 41; claims; example PREP.7 --- -/--	1,6,8-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2000	21/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/05224

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CHEMICAL ABSTRACTS, vol. 100, no. 28, 1984 Columbus, Ohio, US; abstract no. 174768e. M.F. BRANA ET AL.: "REACTION OF N-(1-OXYDO-4-PYRIDYLMETHYL)-3,5-DIMETHYLBENZAMIDE WITH MALONONITRILE" page 627; XP002127059 abstract & HETEROCYCLES., vol. 22, no. 1, 1984, pages 113-5, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0385-5414	1,6
X	CHEMICAL ABSTRACTS, vol. 84, no. 7, 1976 Columbus, Ohio, US; abstract no. 44112b, page 502; XP002127060 abstract & JP 07 435631 A (KOWA) 25 September 1974 (1974-09-25)	1,6-12
X	CHEMICAL ABSTRACTS, vol. 82, no. 28, 1975 Columbus, Ohio, US; abstract no. 171028n, page 555; XP002127061 abstract & JP 07 436719 A (MORI) 2 October 1974 (1974-10-02)	1,6,8-12
X	CHEMICAL ABSTRACTS, vol. 83, no. 28, 1975 Columbus, Ohio, US; abstract no. 10127z, page 853; XP002127062 abstract & JP 07 435633 A (MORI) 25 September 1974 (1974-09-25)	1,6,8-12
X	H.SKULNICK ET AL.: "PYRIMIDINONES.1." JOURNAL OF MEDICINAL CHEMISTRY., vol. 28, no. 12, 1985, pages 1864-9, XP002127057 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 1867 -page 1868; table 1	1,6,8-12

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H.-J. KABBE: "SUBSTITUIERTE 4-HYDROXY- U. 4-AMINO-PYRIMIDINE." JUSTUS LIEBIGS ANNALEN DER CHEMIE., vol. 704, 1967, pages 144-9, XP002127058 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0075-4617 page 144 -page 148	1,6

INTERNATIONAL SEARCH REPORT

...on on patent family members

...onal Application No
PC../JP 99/05224

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9824782 A	11-06-1998	AU 5525498 A	29-06-1998
		AU 6012098 A	29-06-1998
		EP 0948496 A	13-10-1999
		EP 0948497 A	13-10-1999
		WO 9824780 A	11-06-1998
EP 168262 A	15-01-1986	JP 61044872 A	04-03-1986
		US 4725600 A	16-02-1988
JP 7435631 A		NONE	
JP 7436719 A		NONE	
JP 7435633 A		NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

9621 PATENT ATTORNEY IMAMURA M.
9263 PATENT ATTORNEY SHIOZAWA H.
9584 PATENT ATTORNEY KAMATA J.
5th Floor, KRF Bldg., 5-5,
Kyobashi 1-chome
Chuo-ku, Tokyo 104-0031
JAPON

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.12.2000
Applicant's or agent's file reference 99298M	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/05224	24/09/1999	25/09/1998

Applicant
MITSUBISHI CHEMICAL CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Exner, K Tel.+49 89 2399-7826

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
13 October 1999 (13.10.99)	
Applicant's or agent's file reference	**International application No.**
99298M	PCT/JP99/05224

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

MITSUBISHI CHEMICAL CORPORATION (for all designated States except US)
WATANABE, Kazutoshi et al (for US)

International filing date	:	24 September 1999 (24.09.99)
Priority date(s) claimed	:	25 September 1998 (25.09.98) 27 October 1998 (27.10.98)
Date of receipt of the record copy by the International Bureau	:	08 October 1999 (08.10.99)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [X] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Susumu Kubo

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON

00. 2. 7 M12

Date of mailing (day/month/year) 14 January 2000 (14.01.00)	
Applicant's or agent's file reference 99298M	**IMPORTANT NOTIFICATION**
International application No. PCT/JP99/05224	International filing date (day/month/year) 24 September 1999 (24.09.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 September 1998 (25.09.98)
Applicant MITSUBISHI CHEMICAL CORPORATION et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 Sept 1998 (25.09.98)	10/271277	JP	06 Janu 2000 (06.01.00)
27 Octo 1998 (27.10.98)	10/305266	JP	06 Janu 2000 (06.01.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Taïeb Akremi

Telephone No. (41-22) 338.83.38

CORRECTED VERSION

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON

RECEIVED
SIKs & Co.

Date of mailing (day/month/year) 01 March 2000 (01.03.00)	
Applicant's or agent's file reference 99298M	**IMPORTANT NOTIFICATION**
International application No. PCT/JP99/05224	**International filing date** (day/month/year) 24 September 1999 (24.09.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SHODA, Aya Mitsubishi Chemical Corporation Yokohama Research Center 1000, Kamoshida-cho Aoba-ku, Yokohama-shi Kanagawa 227-8502 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The applicant/inventor identified in Box 2 should be included on the record as an additional applicant for US and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Susumu Kubo
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON

Date of mailing (day/month/year) 06 December 1999 (06.12.99)	
Applicant's or agent's file reference 99298M	**IMPORTANT NOTIFICATION**
International application No. PCT/JP99/05224	**International filing date** (day/month/year) 24 September 1999 (24.09.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SHIODA, Aya Mitsubishi Chemical Corporation Yokohama Research Center 1000, Kamoshida-cho Aoba-ku, Yokohama-shi Kanagawa 227-8502 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The applicant/inventor identified in Box 2 should be included on the record as an additional applicant for US and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Susumu Kubo Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

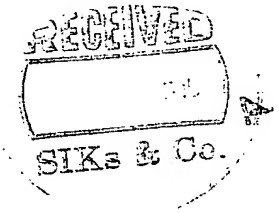
From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON



Date of mailing (day/month/year) 06 April 2000 (06.04.00)	
Applicant's or agent's file reference 99298M	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/JP99/05224	24 September 1999 (24.09.99)	25 September 1998 (25.09.98)

Applicant
MITSUBISHI CHEMICAL CORPORATION et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
   GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
   PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   06 April 2000 (06.04.00) under No. WO 00/18758

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:
IMAMURA, Masazumi
KRF Building
5th floor
5-5, Kyobashi 1-chome
Chuo-ku
Tokyo 104-0031
JAPON

Date of mailing (day/month/year) 06 April 2000 (06.04.00)	
Applicant's or agent's file reference 99298M	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/JP99/05224	24 September 1999 (24.09.99)	25 September 1998 (25.09.98)

Applicant
MITSUBISHI CHEMICAL CORPORATION et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CR,CU,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,
   HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,
   SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

9621 PATENT ATTORNEY IMAMURA M.
9263 PATENT ATTORNEY SHIOZAWA H.
9584 PATENT ATTORNEY KAMATA J.
5th Floor, KRF Bldg., 5-5,
Kyobashi 1-chome
Chuo-ku, Tokyo 104-0031
JAPON

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	09.05.2000
Applicant's or agent's file reference: 99298M	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/05224	24/09/1999	25/09/1998

International Patent Classification (IPC) or both national classification and IPC

C07D401/04

Applicant

MITSUBISHI CHEMICAL CORPORATION et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 25/01/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Baston, E

Formalities officer (incl. extension of time limits)
Luck, E
Telephone No. +49 89 2399 8238

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-96 as originally filed

Claims, No.:

1-12 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

To section V

The following documents have been considered for the examination of the present application:

D1: WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application

D2: EP-A-0 168 262 (FUJISAWA) 15 January 1986 (1986-01-15)

D3: CHEMICAL ABSTRACTS, vol. 100, no. 28, 1984 Columbus, Ohio, US; abstract no. 174768e, M.F. BRANA ET AL.: 'REACTION OF N-(1-OXYDO-4-PYRIDYLMETHYL)-3,5-DIMETHYLBE NZAMIDE WITH MALONONITRILE' page 627; XP002127059 & HETEROCYCLES., vol. 22, no. 1, 1984, pages 113-5, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0385-5414

D4: JP 49-35631 (KOWA) 25 September 1974 (1974-09-25)

D5: CHEMICAL ABSTRACTS, vol. 82, no. 28, 1975 Columbus, Ohio, US; abstract no. 171028n, page 555; XP002127061 & JP 07 436719 A (MORI) 2 October 1974 (1974-10-02)

D6: CHEMICAL ABSTRACTS, vol. 83, no. 28, 1975 Columbus, Ohio, US; abstract no. 10127z, page 853; XP002127062 & JP 07 435633 A (MORI) 25 September 1974 (1974-09-25)

D7: H.SKULNICK ET AL.: 'PYRIMIDINONES.1.' JOURNAL OF MEDICINAL CHEMISTRY., vol. 28, no. 12, 1985, pages 1864-9, XP002127057 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623

D8: H.-J. KABBE: 'SUBSTITUIERTE 4-HYDROXY- U. 4-AMINO-PYRIMIDINE.' JUSTUS LIEBIGS ANNALEN DER CHEMIE., vol. 704, 1967, pages 144-9, XP002127058 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0075-4617

The subject-matter of claims 1-7 cannot be considered novel, since compounds falling in the scope of these claims are already anticipated by the prior art, as indicated below:

Claim 1:

D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40; D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3; D 7: Compounds 108-113, table 1, page 1867; D 8: Compound 4 t, table 1, page 1967.

Claim 2:

D 1: Compounds line 13-14, page 71; D 2: Preparation 7, page 40; D 4: Compounds 2-7, table, page 3; D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1,

page 1967.

Claim 3:

D 2: Preparation 7, page 40; D 4: Compounds 2-7, table, page 3; D 8: Compound 4 t, table 1, page 1967.

Claim 4:

D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40;
D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3;
D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1, page 1967.

Claim 5:

D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40;
D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3;
D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1, page 1967.

Claim 6:

D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40;
D 3: Compound I, mentioned in the abstract; D 4:Compounds 2 and 4, table, page 3;
D 7: Compounds 112-113, page 1867; D 8: Compound 4 t, table 1, page 1967.

Claim 7:

D 4: Compound 2, table, page 3.

Additionally a further relevance of documents D 5 and/or D 6 for the novelty of claims 1,2,4-6 cannot be excluded as indicated below:

Claim 1: D 5: Compounds I and II of the abstract; D 6: Abstract.

Claim 2: D 6: Abstract.

Claim4: D 5: Abstract.

Claim 5: D 5: Abstract.

Claim 6: D 5: Compound I and II of the abstract.

The subject-matter of claims 8-12 cannot be considered novel, since compounds (≡ medicaments) of general formula I are already anticipated by the prior art as indicated above.

No document of the prior art mentions tau protein kinase 1 inhibitory potency for compounds of general formula I. Novelty and the involvment of an inventive step could therefore be attributed to the use of these compounds for the manufacture of a medicament for the treatment of diseases associated with tau protein kinase I hyperactivity.

PCT REQUEST

99298M

Original (for SUBMISSION) - printed on 24.09.1999 02:28:27 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	PCT 24.9.99 受領印
0-3	Name of receiving Office and "PCT International Application"	

0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.84 (updated 01.07.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Japanese Patent Office (RO/JP)
0-7	**Applicant's or agent's file reference**	99298M
I	**Title of invention**	PYRIMIDONE DERIVATIVES
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9 II-10	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No. e-mail	 applicant only all designated States except US MITSUBISHI CHEMICAL CORPORATION 5-2, Marunouchi 2-chome Chiyoda-ku, Tokyo 100-0005 Japan JP JP 03-3283-6977 03-3283-6984 BISICH J24901
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only WATANABE, Kazutoshi c/o MITSUBISHI CHEMICAL CORPORATION, YOKOHAMA RESEARCH CENTER, 1000, Kamoshida-cho Aoba-ku, Yokohama-shi, Kanagawa 227-8502 Japan JP JP

† SHODA Aya

PCT REQUEST 99298M

Original (for **SUBMISSION**) - printed on 24.09.1999 02:28:27 PM

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ANDO, Ryoichi
III-2-5	Address:	c/o MITSUBISHI CHEMICAL CORPORATION, YOKOHAMA RESEARCH CENTER, 1000, Kamoshida-cho Aoba-ku, Yokohama-shi, Kanagawa 227-8502 Japan
III-2-6	State of nationality	JP
III-2-7	State of residence	JP
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	SAITO, Ken-ichi
III-3-5	Address:	c/o MITSUBISHI CHEMICAL CORPORATION, YOKOHAMA RESEARCH CENTER, 1000, Kamoshida-cho Aoba-ku, Yokohama-shi, Kanagawa 227-8502 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KAWAMOTO, Rie
III-4-5	Address:	c/o MITSUBISHI CHEMICAL CORPORATION, YOKOHAMA RESEARCH CENTER, 1000, Kamoshida-cho Aoba-ku, Yokohama-shi, Kanagawa 227-8502 Japan
III-4-6	State of nationality	JP
III-4-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	IMAMURA, Masazumi
IV-1-2	Address:	5th Floor, KRF Bldg., 5-5, Kyobashi 1-chome Chuo-ku, Tokyo 104-0031 Japan
IV-1-3	Telephone No.	03-3271-1331
IV-1-4	Facsimile No.	03-3271-1410

PCT REQUEST 99298M

Original (for **SUBMISSION**) - printed on 24.09.1999 02:28:27 PM

IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	SHIOZAWA, Hisao; KAMATA, Junji
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made unde items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	25 September 1998 (25.09.1998)
VI-1-2	Number	10-271277
VI-1-3	Country	JP

PCT REQUEST 99298M

Original (for SUBMISSION) - printed on 24.09.1999 02:28:27 PM

VI-2	**Priority claim of earlier national application**		
VI-2-1	Filing date	27 October 1998 (27.10.1998)	
VI-2-2	Number	10-305266	
VI-2-3	Country	JP	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	–
VIII-2	Description	96	–
VIII-3	Claims	4	–
VIII-4	Abstract	1	99298m.txt
VIII-5	Drawings	0	–
VIII-7	TOTAL	106	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	–
VIII-9	Separate signed power of attorney		–
VIII-16	PCT-EASY diskette	–	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	IMAMURA, Masazumi M. Imamura	
IX-2	**Signature of applicant or agent**		
IX-2-1	Name (LAST, First)	SHIOZAWA, Hisao H. Shiozawa	
IX-3	**Signature of applicant or agent**		
IX-3-1	Name (LAST, First)	KAMATA, Junji Junji Kamata	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

PCT REQUEST

99298M

Original (for **SUBMISSION**) - printed on 24.09.1999 02:28:27 PM

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PCT (ANNEX - FEE CALCULATION SHEET)

99298M

Original (for **SUBMISSION**) - printed on 24.09.1999 02:28:27 PM

(This sheet is not part of and does not count as a sheet of the international application)

0 0-1	**For receiving Office use only** International Application No.	
0-2	Date stamp of the receiving Office	

0-4 0-4-1	**Form - PCT/RO/101 (Annex)** **PCT Fee Calculation Sheet** Prepared using		PCT-EASY Version 2.84 (updated 01.07.1999)		
0-9	**Applicant's or agent's file reference**		99298M		
2	**Applicant**		MITSUBISHI CHEMICAL CORPORATION, et al.		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (JPY)	
12-1	Transmittal fee	T	⇨	18,000	
12-2	Search fee	S	⇨	120,000	
12-3	International fee Basic fee (first 30 sheets)	b1	54,800		
12-4	Remaining sheets		76		
12-5	Additional amount	(X)	1,300		
12-6	Total additional amount	b2	98,800		
12-7	b1 + b2 =	B	153,600		
12-8	Designation fees Number of designations contained in international application		81		
12-9	Number of designation fees payable (maximum 10)		10		
12-10	Amount of designation fee	(X)	12,600		
12-11	Total designation fees	D	126,000		
12-12	PCT-EASY fee reduction	R	-16,900		
12-13	Total International fee (B+D-R)	I	⇨	262,700	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	400,700	
12-19	**Mode of payment**		Transmittal fee: revenue stamps Search fee: bank draft International fee: bank draft ~~Priority document fee: revenue stamps~~		

VALIDATION LOG AND REMARKS

13-1-1	**Applicant remarks** **Names**	9621 PATENT ATTORNEY IMAMURA Masazumi
13-1-2	**Applicant remarks** **Names**	9263 PATENT ATTORNEY SHIOZAWA Hisao
13-1-3	**Applicant remarks** **Names**	9584 PATENT ATTORNEY KAMATA Junji

PCT (ANNEX - FEE CALCULATION SHEET) 99298M

Original (for SUBMISSION) - printed on 24.09.1999 02:28:27 PM

13-2-2	Validation messages States	Green? More designations could be made. Please verify.
13-2-6	Validation messages Contents	Green? The international application contains no drawings. Please verify.
		Green? Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
		Green? Priority 2. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
		Yellow Accompanying item "separate signed power of attorney" has not been indicated as enclosed.
13-2-9	Validation messages Annotate	Yellow! All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.
13-2-10	Validation messages For receiving Office/International Bureau use only	Green? Verify electronic data for consistency against printed form.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
99298M		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/05224	24/09/1999	25/09/1998
International Patent Classification (IPC) or national classification and IPC C07D401/04		
Applicant MITSUBISHI CHEMICAL CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/02/2000	12.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baston, E Telephone No. +49 89 2399 2120

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/05224

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-96 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations
see separate sheet

To section V

The following documents were considered for the examination of the present application:

D1: WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application

D2: EP-A-0 168 262 (FUJISAWA) 15 January 1986 (1986-01-15)

D3: CHEMICAL ABSTRACTS, vol. 100, no. 28, 1984 Columbus, Ohio, US; abstract no. 174768e, M.F. BRANA ET AL.: 'REACTION OF N-(1-OXYDO-4-PYRIDYLMETHYL)-3,5-DIMETHYLBE NZAMIDE WITH MALONONITRILE' page 627; XP002127059 & HETEROCYCLES., vol. 22, no. 1, 1984, pages 113-5, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0385-5414

D4: JP 49-35631 (KOWA) 25 September 1974 (1974-09-25)

D5: CHEMICAL ABSTRACTS, vol. 82, no. 28, 1975 Columbus, Ohio, US; abstract no. 171028n, page 555; XP002127061 & JP 07 436719 A (MORI) 2 October 1974 (1974-10-02)

D6: CHEMICAL ABSTRACTS, vol. 83, no. 28, 1975 Columbus, Ohio, US; abstract no. 10127z, page 853; XP002127062 & JP 07 435633 A (MORI) 25 September 1974 (1974-09-25)

D7: H.SKULNICK ET AL.: 'PYRIMIDINONES.1.' JOURNAL OF MEDICINAL CHEMISTRY., vol. 28, no. 12, 1985, pages 1864-9, XP002127057 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623

D8: H.-J. KABBE: 'SUBSTITUIERTE 4-HYDROXY- U. 4-AMINO-PYRIMIDINE.' JUSTUS LIEBIGS ANNALEN DER CHEMIE., vol. 704, 1967, pages 144-9, XP002127058 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0075-4617

The subject-matter of claims 1-7 cannot be considered novel, since compounds falling in the scope of these claims are already anticipated by the prior art, as indicated below:

Claim 1: D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40; D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3; D 7: Compounds 108-113, table 1, page 1867; D 8: Compound 4 t, table 1, page 1967.
Claim 2: D 1: Compounds line 13-14, page 71; D 2: Preparation 7, page 40; D 4: Compounds 2- 7, table, page 3; D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1, page 1967.

Claim 3: D 2: Preparation 7, page 40; D 4: Compounds 2-7, table, page 3; D 8: Compound 4 t, table 1, page 1967.
Claim 4: D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40; D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3; D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1, page 1967.
Claim 5: D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40; D 3: Compound I mentioned in the abstract; D 4: Compounds 2-7, table, page 3; D 7: Compounds 108-113, page 1867; D 8: Compound 4 t, table 1, page 1967.
Claim 6: D 1: Compounds line 7-8 and line 11-14, page 71; D 2: Preparation 7, page 40; D 3: Compound I, mentioned in the abstract; D 4:Compounds 2 and 4, table, page 3; D 7: Compounds 112-113, page 1867; D 8: Compound 4 t, table 1, page 1967.
Claim 7: D 4: Compound 2, table, page 3.

Additionally a further relevance of documents D 5 and/or D 6 for the novelty of claims 1,2,4-6 cannot be excluded as indicated below:
Claim 1: D 5: Compounds I and II of the abstract; D 6: Abstract.
Claim 2: D 6: Abstract.
Claim4: D 5: Abstract.
Claim 5: D 5: Abstract.
Claim 6: D 5: Compound I and II of the abstract.

The subject-matter of claims 8-12 cannot be considered novel (Art. 33(2) PCT), since compounds (=medicaments) of general formula I are already anticipated by the prior art as indicated above.

No document of the prior art mentions tau protein kinase 1 inhibitory potency for compounds of general formula I. The involvment of an inventive step (Art. 33(3) PCT) can therefore be attributed to those parts of the claims, which refer to novel compounds.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 401/04, 409/14, 401/14, A61K 31/506 — A1

(11) International Publication Number: **WO 00/18758**

(43) International Publication Date: 6 April 2000 (06.04.00)

(21) International Application Number: PCT/JP99/05224

(22) International Filing Date: 24 September 1999 (24.09.99)

(30) Priority Data:
10/271277 25 September 1998 (25.09.98) JP
10/305266 27 October 1998 (27.10.98) JP

25 Mar 01/30 mo?

(71) Applicant *(for all designated States except US)*: MITSUBISHI CHEMICAL CORPORATION [JP/JP]; 5-2, Marunouchi 2-chome, Chiyoda-ku, Tokyo 100-0005 (JP).

(72) Inventors; and

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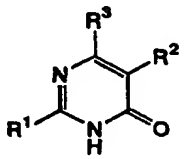

(I)

(57) Abstract

A pyrimidone derivative represented by formula (I) or a salts thereof: wherein R^1 represents an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group and the like; R^2 represents a hydrogen atom, hydroxyl group, an alkyl group, an alkenyl group and the like, R^3 represents a pyridyl group, and a medicament comprising said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase l hyperactivity such as Alzheimer disease.

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PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of tau protein kinase 1, such as Alzheimer disease and the like.

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and amyloid β protein has been elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4,

2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders.

Other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined

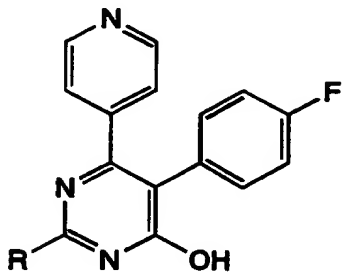
Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of Aβ. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

As structurally similar compounds to the compounds of the present

invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



(A)

wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neutodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

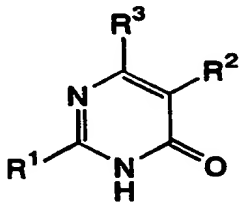
Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease and the like. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment

of the diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of the PHF and by inhibiting the drop of nerve cells.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a C_1-C_{18} alkyloxy group which may be substituted, a C_3-C_{18} alkenyloxy group which may be substituted, a C_3-C_{18} alkynyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a C_6-C_{14} aryloxy group which may be substituted, a heterocyclic group which may be substituted, or a group

represented by $-N(R^4)-W-R^5$ wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted;

R^2 represents hydrogen atom, hydroxyl group, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_1-C_8 alkyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a C_6-C_{14} aryloxy group which may be substituted, a C_1-C_8 alkylthio group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8 dialkylaminocarbonyl group which may be substituted; and

R^3 represents a pyridyl group which may be substituted.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is

used for preventive and/or therapeutic treatment of neurodegenerative diseases. As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives. The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

Best Mode for Carrying Out the Invention

The "alkyl group" or an alkyl portion of a functional group containing the alkyl portion (alkoxyl group, for example) used herein may be either linear or branched. The C_1-C_{18} alkyl group represented by R^1 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group or octadecyl group. In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C_1-C_{18} alkyl group represented by R^1 has one or more substituents A, the alkyl group may have one or more substituents A selected form the group consisting of a C_3-C_8 cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group; a C_6-C_{10} aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group; a C_3-C_8 cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group; fluorenyl group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C_6-C_{14} aryloxy group such as phenoxy group, and naphthoxy group; a C_1-C_5 alkylthio group such as

methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C_6-C_{14} arylthio group such as phenylthio group, and naphthylthio group; a C_1-C_5 alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a C_6-C_{14} arylsulfonyl group such as phenylsulfonyl group, and naphthylsulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C_1-C_5 halogenated alkyl group such as trifluoromethyl group; hydroxyl group; nitro group; oxo group; formyl group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C_1-C_5 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; and a residue of heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring,

phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

When an aryl group or a heterocyclic group is present as a substituent, the group may have one or more substituents B selected form the group consisting of a C_1-C_{18} alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, hexyl group, isohexyl group, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, and octadecyl group, and the aforementioned substituent A.

Examples of the C_3-C_{18} alkenyl group represented by R^1 include, for example, allyl group, 2-butenyl group, 3-butenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 2-methyl-2-butenyl group, 3-methyl-2-butenyl group, 2-hexenyl group, 5-hexenyl group, 2-heptenyl group, 6-heptenyl group, 2-octenyl group, 7-octenyl group, 2-nonenyl group, 8-nonenyl group and the like, and examples of the C_3-C_{18} alkynyl group represented by R^1 include, for example, propargyl group, 2-butynyl group, 3-butynyl group, 2-pentynyl group, 3-pentynyl group, 4-pentynyl group, 1-methyl-2-pentynyl group, 4-methyl-2-pentynyl group, 2-hexynyl group, 5-hexynyl group, 2-heptynyl group, 6-heptynyl group, 2-octynyl group, 7-octynyl group and the like. These groups may be substituted with one or more substituents A.

Examples of the C_3-C_8 cycloalkyl group represented by R^1 include, for

example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like, and examples of the C_6-C_{14} aryl group represented by R^1 include, for example, phenyl group, naphthyl group, anthryl group and the like. These groups may be substituted with one or more substituents B. The C_6-C_{14} aryl group represented by R^1 may further have one or more substituents selected from the group consisting of a hydroxyalkyl group such as hydroxymethyl group, 1-hydroxyethyl group, 2-hydroxyethyl group, and 3-hydroxypropyl group; a C_1-C_3 alkyl group having a C_1-C_6 alkylcarbonyloxy group such as formyloxymethyl group, acetoxymethyl group, 1-acetoxyethyl group, 2-acetoxyethyl group, 3-acetoxypropyl group, propionyloxymethyl group, butyryloxymethyl group, and valeryloxymethyl group; a C_1-C_3 aminoalkyl group such as aminomethyl group, 1-aminoethyl group, 2-aminoethyl group, and 3-aminopropyl group; a monoalkylamino(C_1-C_3 alkyl) group having a C_1-C_8 alkyl group on the nitrogen atom such as methylaminomethyl group, ethylaminomethyl group, 1-methylaminoethyl group, 2-methylaminoethyl group, and 3-methylaminopropyl group; and a dialkylamino(C_1-C_3 alkyl) group having the same or different C_1-C_8 alkyl groups on the nitrogen atom such as dimethylaminomethyl group, diethylaminomethyl group, 1-dimethylaminoethyl group, 2-dimethylaminoethyl group, and 3-dimethylaminopropyl group.

Examples of the C_1-C_{18} alkyloxy group represented by R^1 include, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group, hexyloxy group, isohexyloxy group, heptyloxy group, octyloxy group, nonyloxy group, decyloxy group, undecyloxy group,

dodecyloxy group, tridecyloxy group, tetradecyloxy group, pentadecyloxy group, octadecyloxy group and the like. Examples of the C_3-C_{18} alkenyloxy group represented by R^1 include, for example, allyloxy group, 2-butenyloxy group, 3-butenyloxy group, 2-pentenyloxy group, 3-pentenyloxy group, 4-pentenyloxy group, 2-methyl-2-butenyloxy group, 3-methyl-2-butenyloxy group, 2-hexenyloxy group, 5-hexenyloxy group, 2-heptenyloxy group, 6-heptenyloxy group, 2-octenyloxy group, 7-octenyloxy group, 2-nonenyloxy group, 8-nonenyloxy group and the like. Examples of the C_3-C_{18} alkynyloxy group represented by R^1 include, for example, propargyloxy group, 2-butynyloxy group, 3-butynyloxy group, 2-pentynyloxy group, 3-pentynyloxy group, 4-pentynyloxy group, 1-methyl-2-pentynyloxy group, 4-methyl-2-pentynyloxy group, 2-hexynyloxy group, 5-hexynyloxy group, 2-heptynyloxy group, 6-heptynyloxy group, 2-octynyloxy group, 7-octynyloxy group and the like. These groups may be substituted with one or more substituents A.

Examples of the C_3-C_8 cycloalkyloxy group represented by R^1 include, for example, cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group, and examples of the C_6-C_{14} aryloxy group represented by R^1 include, for example, phenoxy group, naphthoxy group, and anthryloxy group. These groups may be substituted with one or more substituents B.

Examples of the heterocyclic group represented by R^1 include, for example, residues of heterocyclic rings having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring,

isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like. The heterocyclic group may have one or more substituents B.

As the optionally substituted C_1-C_{18} alkyl group, and as the optionally substituted C_3-C_{18} alkenyl group, the optionally substituted C_3-C_{18} alkynyl group, the optionally substituted C_3-C_8 cycloalkyl group, and the optionally substituted C_6-C_{14} aryl group which are independently represented by R^4 and R^5, such as those explained as to R^1 may be used. When the symbol "W" represents nitrogen atom, as the optionally substituted C_1-C_{18} alkyl that may be present on the nitrogen atom, such as those explained as to R^1 may be used.

Examples of the C_1-C_8 alkyl group represented by R^2 include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, n-heptyl group, n-octyl group and the like, and examples of the C_3-C_8 alkenyl group represented by R^2 include, for example, allyl group,

2-butenyl group, 3-butenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 2-methyl-2-butenyl group, 3-methyl-2-butenyl group, 2-hexenyl group, 5-hexenyl group, 2-heptenyl group, 6-heptenyl group, 2-octenyl group, 7-octenyl group and the like. These groups may be have one or more substituents A.

Examples of the C_1-C_8 alkyloxy group represented by R^2 include, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group, hexyloxy group, isohexyloxy group, heptyloxy group, octyloxy group and the like. Examples of the C_1-C_8 alkylthio group represented by R^2 include, for example, methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, sec-butylthio group, tert-butylthio group, pentylthio group, isopentylthio group, neopentyl thio group, 1,1-dimethylpropylthio group, hexylthio group, isohexylthio group, heptylthio group, octylthio group and the like. These groups may be have one or more substituents A.

Examples of the C_1-C_8 alkyloxycarbonyl group represented by R^2 include, for example, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, isopentyloxycarbonyl group, neopentyloxycarbonyl group, 1,1-dimethylpropyloxycarbonyl group, hexyloxycarbonyl group, isohexyloxycarbonyl group, heptyloxycarbonyl group, octyloxycarbonyl group and the like, and examples of the C_3-C_8 cycloalkyloxycarbonyl group represented by R^2 include, for example, cyclopropyloxycarbonyl group, cyclobutyloxycarbonyl group,

cyclopentyloxycarbonyl group, cyclohexyloxycarbonyl group, cycloheptyloxycarbonyl group, cyclooctyloxy carbonyl group and the like. The aforementioned cycloalkyloxycarbonyl groups may have one or more substituents B, and the aforementioned alkyloxycarbonyl groups may have one or more substituents A.

Examples of the C_1-C_8 alkylaminocarbonyl group represented by R^2 include, for example, methylaminocarbonyl group, ethylaminocarbonyl group, propylaminocarbonyl group, isopropylaminocarbonyl group, butylaminocarbonyl group, isobutylaminocarbonyl group, sec-butylaminocarbonyl group, tert-butylaminocarbonyl group, pentylaminocarbonyl group, isopentylaminocarbonyl group, neopentylaminocarbonyl group, 1,1-dimethylpropylaminocarbonyl group, hexylaminocarbonyl group, isohexylaminocarbonyl group, heptylaminocarbonyl group, octylaminocarbonyl group and the like. Examples of the C_1-C_8 dialkylaminocarbonyl group represented by R^2 include, for example, dimethylaminocarbonyl group, diethylaminocarbonyl group, dipropylaminocarbonyl group, diisopropylaminocarbonyl group, dibutylaminocarbonyl group, diisobutylaminocarbonyl group, dipentylaminocarbonyl group, diisopentylaminocarbonyl group, dihexylaminocarbonyl group, diisohexylaminocarbonyl group, diheptylaminocarbonyl group, dioctylaminocarbonyl group and the like. These groups may have one or more substituents A.

As the optionally substituted C_3-C_8 cycloalkyl group, optionally substituted C_3-C_8 cycloalkyloxy group, and optionally substituted C_6-C_{14} aryloxy group represented by R^2, such as those explained as to R^1 may be used. R^3 represents a pyridyl group, which may be any one of 2-pyridyl group, 3-pyridyl group, and 4-pyridyl group. The pyridyl group may have

one or more substituents B.

R^1 may preferably a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted.

More preferably, R^1 may be a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an unsubstituted alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group, or a substituted C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond.

R^2 may preferably be hydrogen atom, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8

dialkylaminocarbonyl group which may be substituted, and more preferably, hydrogen atom, a C_1-C_8 alkyl group, or a halogen atom, and most preferably hydrogen atom. R^3 may preferably be 3-pyridyl group or 4-pyridyl group, and more preferably 4-pyridyl group.

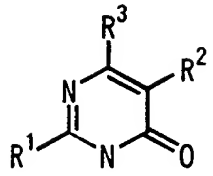
The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S)

configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention. Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound of may exist as tautomers. The existence of such tautomers is readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited by the following compounds.

Table-1



Compound No.	R^1	R^2	R^3
1	Me	H	4-Py
2	Et	H	4-Py
3	n-Pr	H	4-Py
4	i-Pr	H	4-Py
5	n-Bu	H	4-Py
6	i-Bu	H	4-Py
7	sec-Bu	H	4-Py
8	tert-Bu	H	4-Py
9	$n\text{-}C_5H_{11}$	H	4-Py

Table-1(continued)

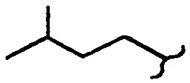
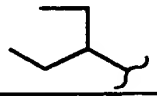
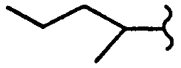
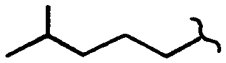
Compound No.	R^1	R^2	R^3
10		H	4-Py
11		H	4-Py
12		H	4-Py
13		H	4-Py
14	n-C_6H_{13}	H	4-Py
15		H	4-Py
16	n-C_7H_{15}	H	4-Py
17	n-C_8H_{17}	H	4-Py
18	n-C_9H_{19}	H	4-Py
19	n-$C_{10}H_{21}$	H	4-Py
20	n-$C_{11}H_{23}$	H	4-Py

Table-1(continued)

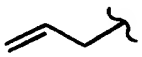
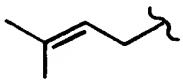
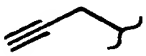
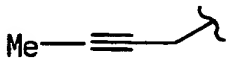
Compound No.	R^1	R^2	R^3
21	n-$C_{12}H_{25}$	H	4-Py
22	n-$C_{13}H_{27}$	H	4-Py
23	n-$C_{14}H_{29}$	H	4-Py
24	n-$C_{15}H_{31}$	H	4-Py
25	n-$C_{16}H_{33}$	H	4-Py
26	n-$C_{17}H_{35}$	H	4-Py
27	n-$C_{18}H_{37}$	H	4-Py
28		H	4-Py
29		H	4-Py
30		H	4-Py
31		H	4-Py

Table-1(continued)

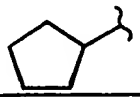
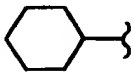
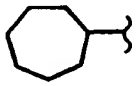
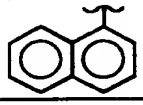
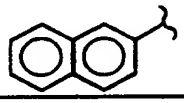
Compound No.	R^1	R^2	R^3
32		H	4-Py
33		H	4-Py
34		H	4-Py
35	Ph	H	4-Py
36		H	4-Py
37		H	4-Py
38	2-Me-Ph	H	4-Py
39	3-Me-Ph	H	4-Py
40	4-Me-Ph	H	4-Py
41	2-Et-Ph	H	4-Py
42	3-Et-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
43	4-Et-Ph	H	4-Py
44	2-F-Ph	H	4-Py
45	3-F-Ph	H	4-Py
46	4-F-Ph	H	4-Py
47	2-Cl-Ph	H	4-Py
48	3-Cl-Ph	H	4-Py
49	4-Cl-Ph	H	4-Py
50	2-Br-Ph	H	4-Py
51	3-Br-Ph	H	4-Py
52	4-Br-Ph	H	4-Py
53	2-MeO-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
54	3-MeO-Ph	H	4-Py
55	4-MeO-Ph	H	4-Py
56	2-EtO-Ph	H	4-Py
57	3-EtO-Ph	H	4-Py
58	4-EtO-Ph	H	4-Py
59	2-CN-Ph	H	4-Py
60	3-CN-Ph	H	4-Py
61	4-CN-Ph	H	4-Py
62	2-NO_2-Ph	H	4-Py
63	3-NO_2-Ph	H	4-Py
64	4-NO_2-Ph	H	4-Py

Table-1(continued)

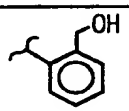
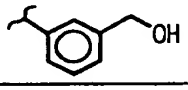
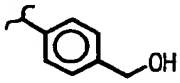
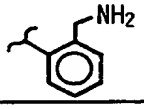
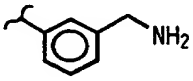
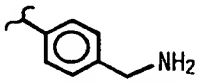
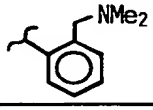
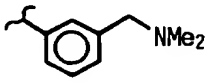
Compound No.	R^1	R^2	R^3
65	2-CF_3-Ph	H	4-Py
66	3-CF_3-Ph	H	4-Py
67	4-CF_3-Ph	H	4-Py
68		H	4-Py
69		H	4-Py
70		H	4-Py
71		H	4-Py
72		H	4-Py
73		H	4-Py
74		H	4-Py
75		H	4-Py

Table-1(continued)

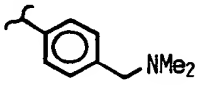
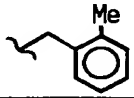
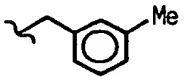
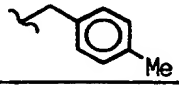
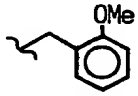
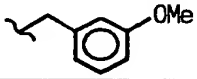
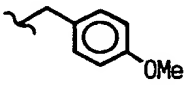
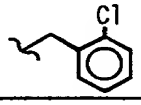
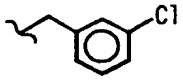
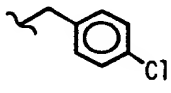
Compound No.	R^1	R^2	R^3
76		H	4-Py
77		H	4-Py
78		H	4-Py
79		H	4-Py
80		H	4-Py
81		H	4-Py
82		H	4-Py
83		H	4-Py
84		H	4-Py
85		H	4-Py
86		H	4-Py

Table-1(continued)

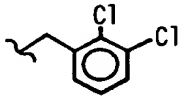
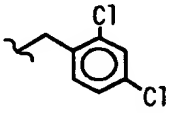
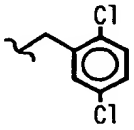
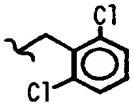
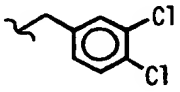
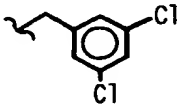
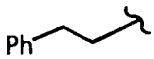
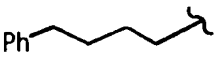
Compound No.	R^1	R^2	R^3
87		H	4-Py
88		H	4-Py
89		H	4-Py
90		H	4-Py
91		H	4-Py
92		H	4-Py
93		H	4-Py
94		H	4-Py
95		H	4-Py

Table-1(continued)

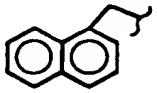
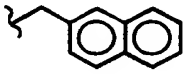
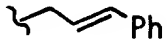
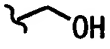
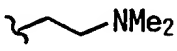
Compound No.	R^1	R^2	R^3
96		H	4-Py
97		H	4-Py
98		H	4-Py
99		H	4-Py
100		H	4-Py
101		H	4-Py
102		H	4-Py
103		H	4-Py
104		H	4-Py
105		H	4-Py
106		H	4-Py

Table-1(continued)

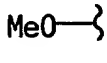
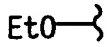
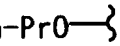
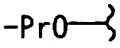
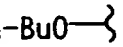
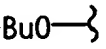
Compound No.	R^1	R^2	R^3
107		H	4-Py
108		H	4-Py
109		H	4-Py
110		H	4-Py
111		H	4-Py
112		H	4-Py
113		H	4-Py
114		H	4-Py
115		H	4-Py
116		H	4-Py
117		H	4-Py

Table-1(continued)

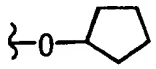
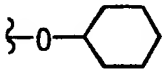
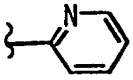
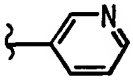
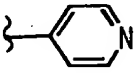
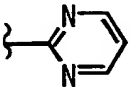
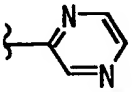
Compound No.	R^1	R^2	R^3
118	t-BuO—	H	4-Py
119	n-C_5H_{11}O—	H	4-Py
120	n-C_6H_{13}O—	H	4-Py
121		H	4-Py
122		H	4-Py
123	—OPh	H	4-Py
124		H	4-Py
125		H	4-Py
126		H	4-Py
127		H	4-Py
128		H	4-Py

Table-1(continued)

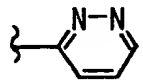
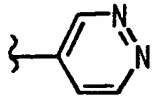
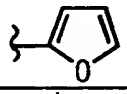
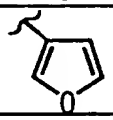
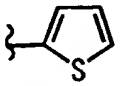
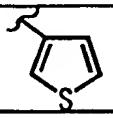
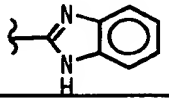
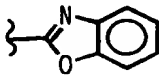
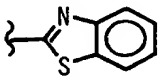
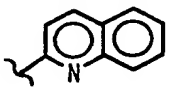
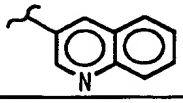
Compound No.	R^1	R^2	R^3
129		H	4-Py
130		H	4-Py
131		H	4-Py
132		H	4-Py
133		H	4-Py
134		H	4-Py
135		H	4-Py
136		H	4-Py
137		H	4-Py
138		H	4-Py
139		H	4-Py

Table-1(continued)

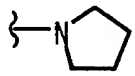
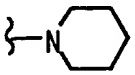
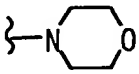
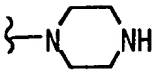
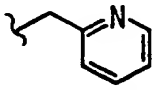
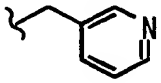
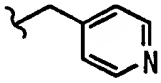
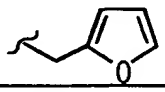
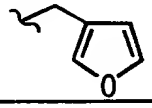
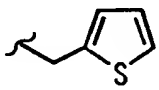
Compound No	R^1	R^2	R^3
140		H	4-Py
141		H	4-Py
142		H	4-Py
143		H	4-Py
144		H	4-Py
145		H	4-Py
146		H	4-Py
147		H	4-Py
148		H	4-Py
149		H	4-Py
150		H	4-Py

Table-1(continued)

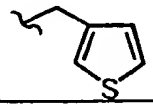
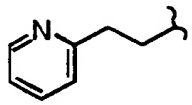
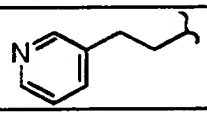
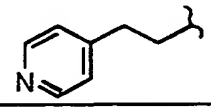
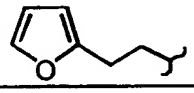
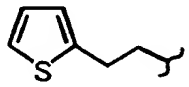
Compound No.	R^1	R^2	R^3
151		H	4-Py
152		H	4-Py
153		H	4-Py
154		H	4-Py
155		H	4-Py
156		H	4-Py
157	NH_2	H	4-Py
158	NHMe	H	4-Py
159	NHEt	H	4-Py
160	NHn-Pr	H	4-Py
161	NHi-Pr	H	4-Py

Table-1(continued)

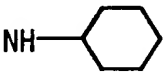
Compound No.	R^1	R^2	R^3
162	NHn-Bu	H	4-Py
163	NHi-Bu	H	4-Py
164	NHt-Bu	H	4-Py
165	NHn-C_5H_{11}	H	4-Py
166	NHn-C_6H_{13}	H	4-Py
167		H	4-Py
168	NHPh	H	4-Py
169	NMe_2	H	4-Py
170	NEt_2	H	4-Py
171	Nn-Pr_2	H	4-Py
172	$NHNH_2$	H	4-Py

Table-1(continued)

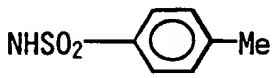
Compound No.	R^1	R^2	R^3
173	NHNHMe	H	4-Py
174	$NHNMe_2$	H	4-Py
175	$NMeNH_2$	H	4-Py
176	$NMeNMe_2$	H	4-Py
177	$NHCOCH_3$	H	4-Py
178	$NHCOC_2H_5$	H	4-Py
179	NHCOPh	H	4-Py
180	$NHSO_2Me$	H	4-Py
181	$NHSO_2Ph$	H	4-Py
182		H	4-Py
183	Ph	Me	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
184		Me	4-Py
185	Ph	Et	4-Py
186		Et	4-Py
187	Ph	n-Pr	4-Py
188		n-Pr	4-Py
189	Ph	i-Pr	4-Py
190		i-Pr	4-Py
191	Ph	n-Bu	4-Py
192		n-Bu	4-Py
193	Ph	i-Bu	4-Py
194		i-Bu	4-Py

Table-1(continued)

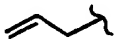
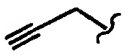
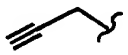
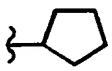
Compound No.	R^1	R^2	R^3
195	Ph	t-Bu	4-Py
196		t-Bu	4-Py
197	Ph	n-C_5H_{11}	4-Py
198		n-C_5H_{11}	4-Py
199	Ph	n-C_6H_{13}	4-Py
200		n-C_6H_{13}	4-Py
201	Ph		4-Py
202			4-Py
203	Ph		4-Py
204			4-Py
205	Ph		4-Py

Table-1(continued)

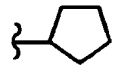
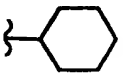
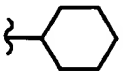
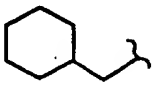
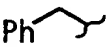
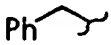
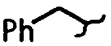
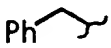
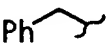
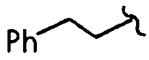
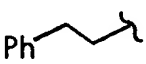
Compound No.	R^1	R^2	R^3
206			4-Py
207	Ph		4-Py
208			4-Py
209			4-Py
210			4-Py
211	Me		4-Py
212	Ph		4-Py
213			4-Py
214	Ph		4-Py
215			4-Py
216	Ph		4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
217			4-Py
218	Ph	OH	4-Py
219		OH	4-Py
220	Ph	OMe	4-Py
221		OMe	4-Py
222	Ph	OEt	4-Py
223		OEt	4-Py
224	Ph	OPh	4-Py
225		OPh	4-Py
226	Ph	SMe	4-Py
227		SMe	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
228	Ph	F	4-Py
229		F	4-Py
230	Ph	Cl	4-Py
231		Cl	4-Py
232	NH_2	Cl	4-Py
233	Ph	Br	4-Py
234		Br	4-Py
235	Ph	NO_2	4-Py
236		NO_2	4-Py
237	Ph	CN	4-Py
238		CN	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
239	Ph	NH_2	4-Py
240		NH_2	4-Py
241	Ph	NMe_2	4-Py
242		NMe_2	4-Py
243	Ph	-COOH	4-Py
244		-COOH	4-Py
245	Ph	-COOMe	4-Py
246		-COOMe	4-Py
247	Ph	-COOEt	4-Py
248		-COOEt	4-Py
249	Ph	$CONH_2$	4-Py

Table-1(continued)

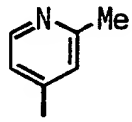
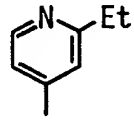
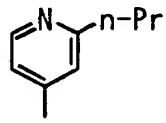
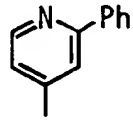
Compound No.	R^1	R^2	R^3
250		$CONH_2$	4-Py
251	Ph	$CONMe_2$	4-Py
252		$CONMe_2$	4-Py
253	Ph	H	
254		H	
255	Ph	H	
256		H	
257	Ph	H	
258		H	
259	Ph	H	
260		H	

Table-1(continued)

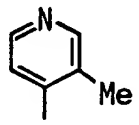
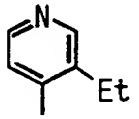
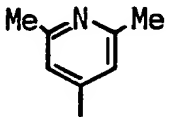
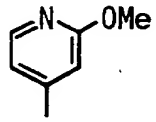
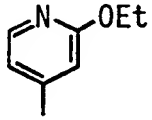
Compound No.	R^1	R^2	R^3
261	Ph	H	
262		H	
263	Ph	H	
264		H	
265	Ph	H	
266		H	
267	Ph	H	
268		H	
269	4-Py	H	
270	Ph	H	
271		H	

Table-1(continued)

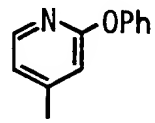
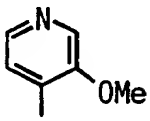
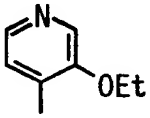
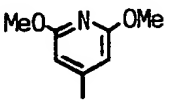
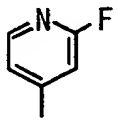
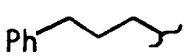
Compound No.	R^1	R^2	R^3
272	Ph	H	
273		H	
274	Ph	H	
275		H	
276	Ph	H	
277		H	
278	Ph	H	
279		H	
280	Ph	H	
281		H	

Table-1(continued)

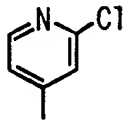
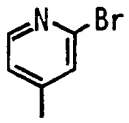
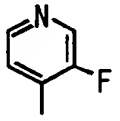
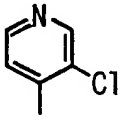
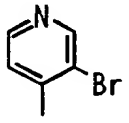
Compound No.	R^1	R^2	R^3
282	Ph	H	
283		H	
284	4-Py	H	
285	Ph	H	
286		H	
287	Ph	H	
288		H	
289	Ph	H	
290		H	
291	Ph	H	
292		H	

Table-1(continued)

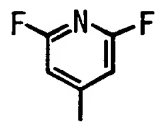
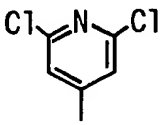
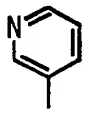
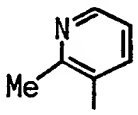
Compound No.	R^1	R^2	R^3
293	Ph	H	
294		H	
295	Ph	H	
296		H	
297	Me	H	
298	Ph	H	
299		H	
300	4-Py	H	
301	NMe_2	H	
302	Ph	H	
303		H	

Table-1(continued)

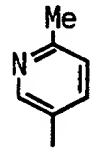
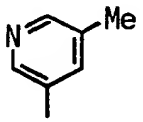
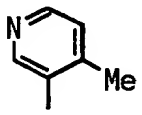
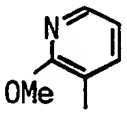
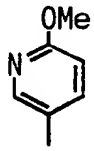
Compound No.	R^1	R^2	R^3
304	Ph	H	
305		H	
306	Ph	H	
307		H	
308	Ph	H	
309		H	
310	Ph	H	
311		H	
312	Ph	H	
313		H	

Table-1(continued)

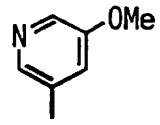
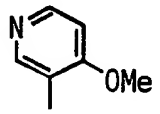
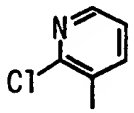
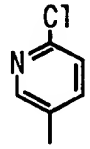
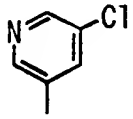
Compound No	R^1	R^2	R^3
314	Ph	H	
315		H	
316	Ph	H	
317		H	
318	Ph	H	
319		H	
320	Ph	H	
321		H	
322	Ph	H	
323		H	

Table-1(continued)

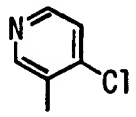
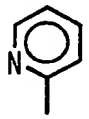
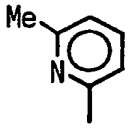
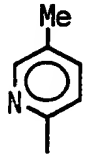
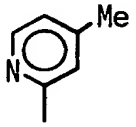
Compound No.	R^1	R^2	R^3
324	Ph	H	
325		H	
326	Ph	H	
327		H	
328	Ph	H	
329		H	
330	Ph	H	
331		H	
332	Ph	H	
333		H	

Table-1(continued)

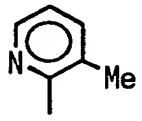
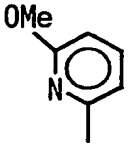
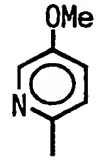
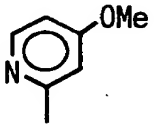
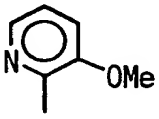
Compound No.	R^1	R^2	R^3
334	Ph	H	
335		H	
336	Ph	H	
337		H	
338	Ph	H	
339		H	
340	Ph	H	
341		H	
342	Ph	H	
343		H	

Table-1(continued)

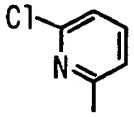
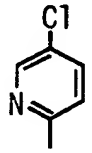
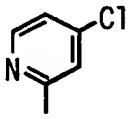
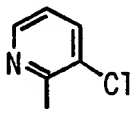
Compound No.	R^1	R^2	R^3
344	Ph	H	
345		H	
346	Ph	H	
347		H	
348	Ph	H	
349		H	
350	Ph	H	
351		H	
352	2-n-Pr-Ph	H	4-Py
353	2-i-Pr-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
354	2-n-Bu-Ph	H	4-Py
355	2-i-Bu-Ph	H	4-Py
356	2-sec-Bu-Ph	H	4-Py
357	2-tert-Bu-Ph	H	4-Py
358	2-n-C_5H_{11}-Ph	H	4-Py
359	2-n-C_6H_{13}-Ph	H	4-Py
360	2-Ph-Ph	H	4-Py
361	3-n-Pr-Ph	H	4-Py
362	3-i-Pr-Ph	H	4-Py
363	3-n-Bu-Ph	H	4-Py
364	3-i-Bu-Ph	H	4-Py

Table-1(continued)

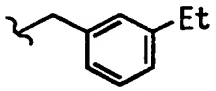
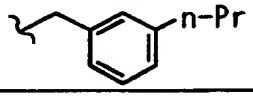
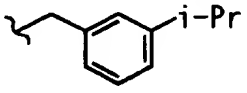
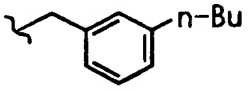
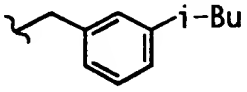
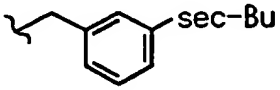
Compound No.	R^1	R^2	R^3
365	3-sec-Bu-Ph	H	4-Py
366	3-tert-Bu-Ph	H	4-Py
367	3-n-C_5H_{11}-Ph	H	4-Py
368	3-n-C_6H_{13}-Ph	H	4-Py
369	3-Ph-Ph	H	4-Py
370		H	4-Py
371		H	4-Py
372		H	4-Py
373		H	4-Py
374		H	4-Py
375		H	4-Py

Table-1(continued)

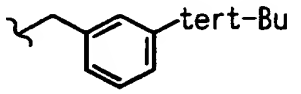
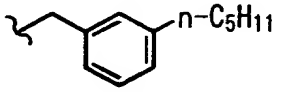
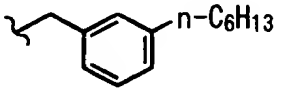
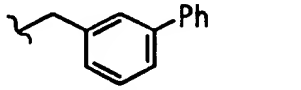
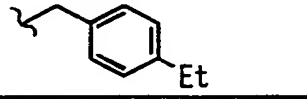
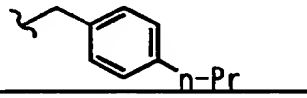
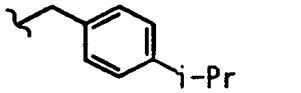
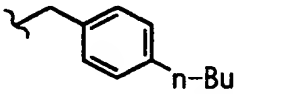
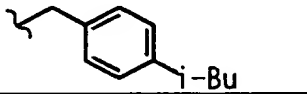
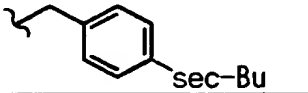
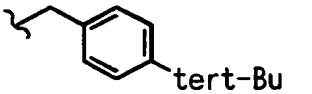
Compound No.	R^1	R^2	R^3
376		H	4-Py
377		H	4-Py
378		H	4-Py
379		H	4-Py
380		H	4-Py
381		H	4-Py
382		H	4-Py
383		H	4-Py
384		H	4-Py
385		H	4-Py
386		H	4-Py

Table-1(continued)

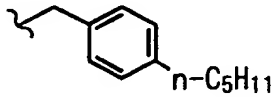
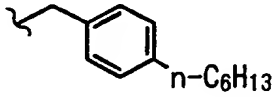
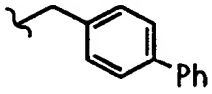
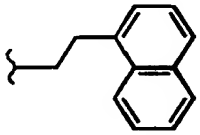
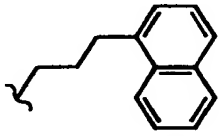
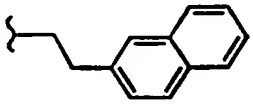
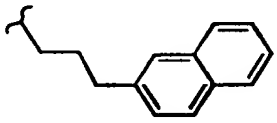
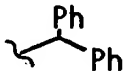
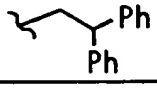
Compound No.	R^1	R^2	R^3
387		H	4-Py
388		H	4-Py
389		H	4-Py
390		H	4-Py
391		H	4-Py
392		H	4-Py
393		H	4-Py
394		H	4-Py
395		H	4-Py

Table-1(continued)

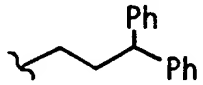
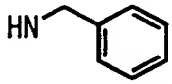
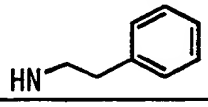
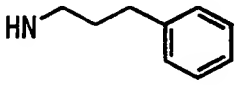
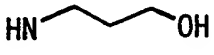
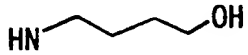
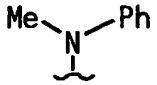
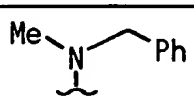
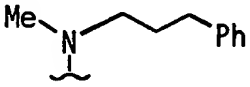
Compound No.	R^1	R^2	R^3
396		H	4-Py
397		H	4-Py
398		H	4-Py
399		H	4-Py
400		H	4-Py
401		H	4-Py
402		H	4-Py
403		H	4-Py
404		H	4-Py
405		H	4-Py
406		H	4-Py

Table-1(continued)

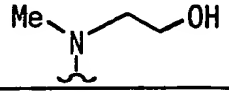
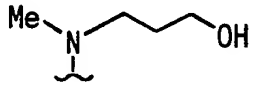
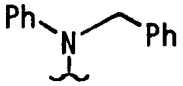
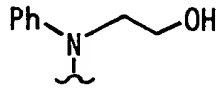
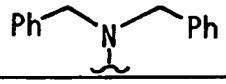
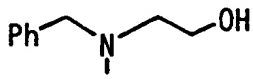
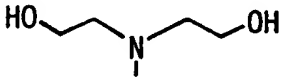
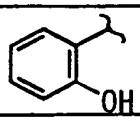
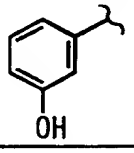
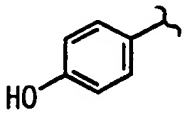
Compound No.	R^1	R^2	R^3
407		H	4-Py
408		H	4-Py
409		H	4-Py
410		H	4-Py
411		H	4-Py
412		H	4-Py
413		H	4-Py
414		H	4-Py
415		H	4-Py
416		H	4-Py

Table-1(continued)

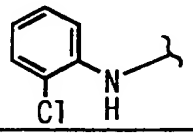
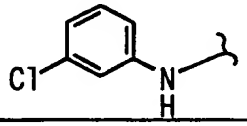
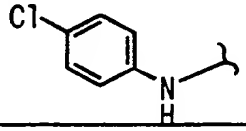
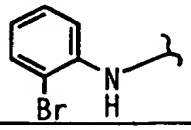
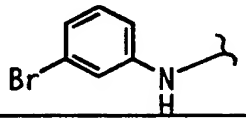
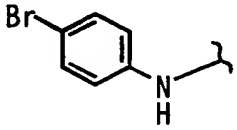
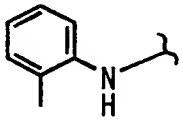
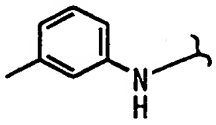
Compound No.	R^1	R^2	R^3
417		H	4-Py
418		H	4-Py
419		H	4-Py
420		H	4-Py
421		H	4-Py
422		H	4-Py
423		H	4-Py
424		H	4-Py

Table-1(continued)

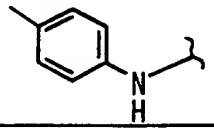
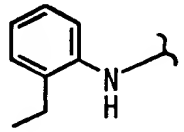
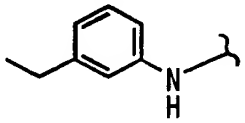
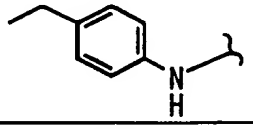
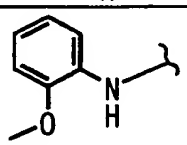
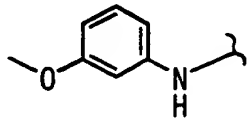
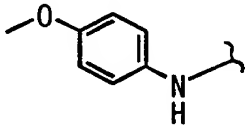
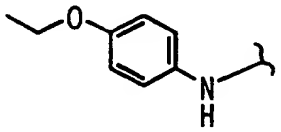
Compound No.	R^1	R^2	R^3
425		H	4-Py
426		H	4-Py
427		H	4-Py
428		H	4-Py
429		H	4-Py
430		H	4-Py
431		H	4-Py
432		H	4-Py

Table-1(continued)

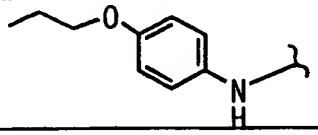
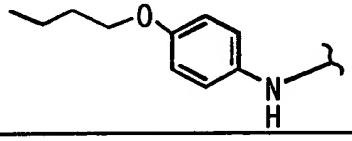
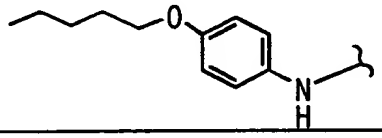
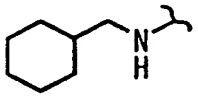
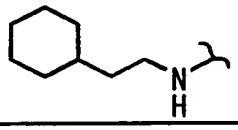
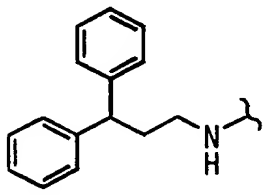
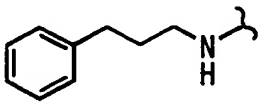
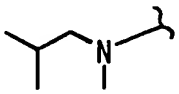
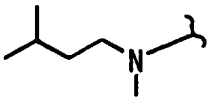
Compound No.	R^1	R^2	R^3
433		H	4-Py
434		H	4-Py
435		H	4-Py
436		H	4-Py
437		H	4-Py
438		H	4-Py
439		H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
440		H	4-Py
441		H	4-Py

Particularly preferred compounds of the present invention represented by formula (I) include:

(1) compounds wherein R^2 is hydrogen atom, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8 dialkylaminocarbonyl group which may be substituted;

(2) compounds wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted;

(3) compounds wherein R^2 is hydrogen atom, a C_1-C_8 alkyl group, or a halogen atom;

(4) compounds wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an unsubstituted alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond;

(5) compounds wherein R^2 is hydrogen atom;

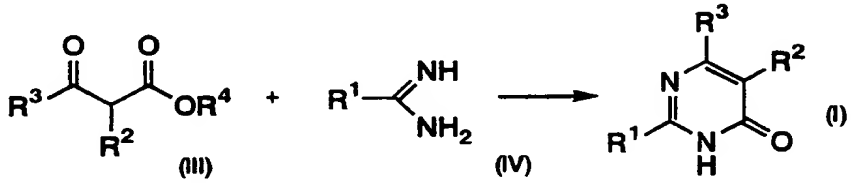
(6) compounds wherein R^3 represents a 3-pyridyl group which may be

substituted or a 4-pyridyl group which may be substituted; and

(7) compounds wherein R^3 represents a 4-pyridyl group which may be substituted.

The pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.

<Preparation Method 1>



(In the above scheme, R^4 represents an alkyl group which may be substituted and definitions of R^1 - R^3 are the same as those already described.)

The 3-ketoester represented by the above formula(III) is allowed to react with the compound represented by formula(IV) or a salt thereof to obtain the compound of the aforementioned formula(I) in the presence of a base such as lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, 1,8-diazabicyclo[5,4,0]undec-7-en, triethylamine, diisopropylethylamine, dimethylbenzylamine, dimethylaniline, diethylaniline and the like. Compounds of formula(III) and formula(IV) are commercially available or may be synthesized according to known methods of one skilled in the art. Compound of formula(I) could be derivatised into other compound of formula(I), using well known method in the art.

Examples of a solvent include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated

solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetoaminde, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used, and the reaction may be carried out for 1 minute to 14 days at a suitable temperature ranging from 0℃ to 250℃ under nitrogen or argon atmosphere or in under ordinary air. In the above reaction, protection or deprotection of a functional group may sometimes be necessary. A suitable protective group can be chosen depending on the type of a functional group, and a method described in the literature may be applied as experimental procedures.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in Alzheimer disease and the like, thereby suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia and the like.

As the active ingredient of the medicament of the present invention,

a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a

daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Preparation of 2-(3-pyridyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 125)

ethyl 3-(4-pyridyl)-3-oxopropionate (0.60 g), 3-amidinopyridine hydrochloride (0.54 g) and potassium carbonate (1.15 g) were added to 5 ml of ethanol, and the mixture was heated under reflux at 75 °C for 20 hours. Acetic acid was added to the reaction mixture, and the solvent was removed by distillation. The residue was added with water and then with acetic acid, and the resulting solid was separated by filtration, washed with water and ethyl acetate, and dried to obtain 0.39 g of the desired compound.

Yield: 50%.

Melting Point: >300°C.

NMR (DMSO-d_6, δ): 7.21 (1H, s), 7.59-7.63 (1H, m), 8.16 (2H, dd, J=1.5, 4.7Hz), 8.59-8.62 (1H, m), 8.74-8.79 (3H, m), 9.41 (1H, d, J=1.8Hz).

Compounds of Example 2 to 63 were prepared in a similar manner to that in Example 1. Physical properties of the compounds are shown below.

Example 2: Preparation of 2-methyl-6-(4-pyridyl)pyrimidin-4-one (Compound 1)

Melting Point: >300°C.

NMR (DMSO-d_6, δ): 2.38 (3H, s), 6.94 (1H, s), 7.98 (2H, dd, J=1.9, 4.5Hz), 8.69 (2H, dd, J=1.9,4.6Hz).

Example 3: Preparation of 2-ethyl-6-(4-pyridyl)pyrimidin-4-one (Compound 2)

Melting Point: 265-269°C.

NMR (DMSO-d_6, δ): 1.26 (3H, t, J=7.5Hz), 2.65 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.99 (2H, dd, J=1.8, 4.6Hz), 8.69 (2H, dd, J=1.4, 4.6Hz).

Example 4: Preparation of 2-propyl-6-(4-pyridyl)pyrimidin-4-one (Compound 3)

Melting Point: >300°C.

NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.5Hz), 1.70-1.83 (2H, m), 2.61 (2H, t, J=7.8Hz), 6.95 (1H, s), 7.99 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.8, 4.8Hz), 12.64 (1H, bs).

Example 5: Preparation of 2-isopropyl-6-(4-pyridyl)pyrimidin-4-one (Compound 4)

Melting Point: 250-252°C.

NMR (DMSO-d_6, δ): 1.27 (6H, d, J=7.2Hz), 2.86-2.95 (1H, m), 6.91 (1H, s), 8.00 (2H, dd, J=1.5, 4.2Hz), 8.70 (2H, dd, J=1.5, 4.5Hz).

Example 6: Preparation of 2-butyl-6-(4-pyridyl)pyrimidin-4-one (Compound 5)

Melting Point:282-285°C.

NMR (DMSO-d_6, δ): 0.92 (3H, t, J=7.5Hz), 1.32-1.40 (2H, m), 1.67-1.75 (2H, m), 2.63 (2H, t, J=7.5Hz), 6.94 (1H, s), 7.98 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.2Hz), 12.59 (1H, bs).

Example 7: Preparation of 2-isobutyl-6-(4-pyridyl)pyrimidin-4-one (Compound 6)

Melting Point:280-283°C.

NMR (DMSO-d_6, δ): 0.95 (6H, d, J=6.6Hz), 2.16-2.25 (1H, m), 2.51 (2H, d, J=7.2Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.8, 4.5Hz), 8.70 (2H, dd, J=1.8, 4.5Hz), 12.59 (1H, bs).

Example 8: Preparation of 2-pentyl-6-(4-pyridyl)pyrimidin-4-one (Compound 9)

Melting Point:238-240°C.

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6Hz), 1.24-1.38 (4H, m), 1.78-1.90 (2H, m), 2.62 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.5Hz).

Example 9: Preparation of 2-hexyl-6-(4-pyridyl)pyrimidin-4-one (Compound 14)

Melting Point:226-229°C.

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9Hz), 1.21-1.38 (6H, m), 1.68-1.78 (2H, m), 2.62 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.8, 4.5Hz), 8.70 (2H,

dd, J=1.5, 4.5Hz), 12.60 (1H, bs).

Example 10: Preparation of 2-heptyl-6-(4-pyridyl)pyrimidin-4-one (Compound 16)

Melting Point: 219-220℃.

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.8Hz), 1.19-1.37 (8H, m), 1.69-1.78 (2H, m), 2.62 (2H, t, J=7.3Hz), 6.92 (1H, s), 7.98 (2H, dd, J=1.4, 4.6Hz), 8.69 (2H, dd, J=1.9, 4.6Hz).

Example 11: Preparation of 2-octyl-6-(4-pyridyl)pyrimidin-4-one (Compound 17)

Melting Point:197-200℃.

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.9Hz), 1.10-1.37 (10H, m), 1.67-1.78 (2H, m), 2.61 (2H, t, J=7.5Hz), 6.89 (1H, s), 7.98 (2H, dd, J=1.8, 4.5Hz), 8.68 (2H, dd, J=1.5, 4.5Hz).

Example 12: Preparation of 2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 35)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.14 (1H, s), 7.55-7.78 (3H, m), 8.14 (2H, dd, J=1.4, 4.6Hz), 8.26-8.29 (2H, m), 8.75 (2H, dd, J=1.7, 4.6Hz).

Example 13: Preparation of 2-(1-naphthyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 36)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.20 (1H, s), 7.60-7.69 (3H, m), 7.80-7.86 (1H, m), 8.00-8.08 (3H, m), 8.10-8.18 (1H, m), 8.19-8.27 (1H, m), 8.71 (H, dd, J=1.6,

4.4Hz).

Example 14: Preparation of 6-(4-pyridyl)-2-(2-tolyl)pyrimidin-4-one (Compound 38)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.44 (3H, s), 7.12 (1H, s), 7.29-7.38 (2H, m), 7.40-7.48 (1H, m), 7.50-7.58 (1H, m), 8.03 (2H, d, J=6.3Hz), 8.71 (2H, d, J=6.0Hz), 12.90 (1H, s).

Example 15: Preparation of 6-(4-pyridyl)-2-(3-tolyl)pyrimidin-4-one (Compound 39)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.42 (3H, s), 7.11 (1H, s), 7.44-7.49 (2H, m), 8.01-8.09 (2H, m), 8.12 (2H, dd, J=1.5, 4.5Hz), 8.75 (2H, dd, J=1.5, 4.5Hz).

Example 16: Preparation of 6-(4-pyridyl)-2-(4-tolyl)pyrimidin-4-one (Compound 40)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.41 (3H, s), 7.08 (1H, s), 7.38 (2H, d, J=8.1Hz), 8.12 (2H, dd, J=1.5, 4.5Hz), 8.18 (2H, d, J=8.1Hz), 8.74 (2H, d, J=1.5, 4.8Hz).

Example 17: Preparation of 2-(4-fluorophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 46)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.06 (1H, s), 7.35-7.41 (2H, m), 8.11 (2H, dd, J=1.7, 4.5Hz), 8.36-8.39 (2H, m), 8.73 (2H, dd, J=1.6, 4.6Hz).

Example 18: Preparation of 2-(4-chlorophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 49)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.15 (1H, s), 7.63 (2H, d, J=8.7Hz), 8.13 (2H, dd, J=1.5, 4.5Hz), 8.31 (2H, d, J=8.7Hz), 8.75 (2H, d, J=6.0Hz).

Example 19: Preparation of 2-(3-bromophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 51)

Melting Point: 285-287℃.

NMR (DMSO-d_6, δ): 7.19 (1H, s), 7.52-7.57 (1H, m). 7.81-7.84 (1H, m), 8.14 (2H, dd, J=1.5, 4.5Hz). 8.28-8.32 (1H, m), 8.42-8.48 (1H, m), 8.75 (2H, dd, J=1.5, 4.8Hz).

Example 20: Preparation of 2-(3-methoxyphenyl)-6-(4-pyridyl)pyrimidin -4-one (Compound 54)

Melting Point: 262-264℃.

NMR (DMSO-d_6, δ): 3.87 (3H, s), 7.11 (1H, s), 7.16-7.20 (1H, m), 7.45-7.51 (1H, m), 7.82 (1H, s). 7.87-7.90 (1H, m), 8.12 (2H, dd. J=1.5. 4.5Hz). 8.74 (2H, dd, J=1.5, 4.5Hz).

Example 21: Preparation of 2-(3-ethoxyphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 57)

Melting Point: 250-253℃.

NMR (DMSO-d_6, δ): 1.38 (3H, t, J=6.9Hz), 4.15 (2H, q. J=6.9Hz), 7.13 (1H, s), 7.15-7.19 (1H, m), 7.44-7.50 (1H, m), 7.80 (1H, s), 7.84-7.88 (1H, m), 8.13 (2H, dd, J=1.5, 4.8Hz). 8.75 (2H, dd, J=1.5. 4.8Hz), 12.92 (1H. bs).

Example 22: Preparation of 2-(3-cyanophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 60)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.76-7.81 (1H, m). 8.07-8.10 (1H, m), 8.18 (2H, dd, J=1.2, 4.5Hz), 8.57-8.62 (1H, m), 8.71-8.77 (3H.m).

Example 23: Preparation of 2-(4-cyanophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 61)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.25 (1H, s), 8.06 (2H, d, J=8.4Hz), 8.16 (2H, dd, J=1.5, 4.5Hz), 8.47 (2H, d, J=8.4Hz), 8.76 (2H, d, J=1.5, 4.8Hz).

Example 24: Preparation of 2-(4-nitrophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 64)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.30 (1H, s), 8.17 (2H, dd, J=1.1, 4.7Hz), 8.40 (2H, d, J=8.8Hz), 8.56 (2H, d, J=8.8Hz), 8.76 (2H, d. J=5.9Hz).

Example 25: Preparation of 6-(4-pyridyl)-2-(3-trifluorophenyl)-pyrimidin -4-one (Compound 66)

NMR (DMSO-d_6, δ): 7.18 (1H, s), 7.78-7.84 (1H, m). 7.95-8.00 (1H, m), 8.13 (2H, dd, J=1.6, 4.5Hz), 8.60-8.63 (2H, m), 8.76 (2H, dd. J=1.6, 4.5Hz).

Example 26: Preparation of 6-(4-pyridyl)-2-(4-trifluorophenyl)-pyrimidin -4-one (Compound 67)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.26 (1H, s). 7.95 (2H. d, J=8.4Hz). 8.15 (2H, dd, J=1.2,

4.8Hz), 8.50 (2H, d, J=8.1Hz), 8.77 (2H, dd, J=0.9, 4.8Hz), 13.09 (1H, bs).

Example 27: Preparation of 2-(3-(dimethylaminomethyl)phenyl)-6-(4-pyridyl) pyrimidin-4-one dihydrochloride (Compound 75)

Melting Point: 185-190℃.

NMR (DMSO-d_6, δ): 2.75 (6H, d, J=4.8Hz), 4.40 (2H, d, J=5.1Hz), 7.36 (1H, s), 7.68 (1H, t, J=7.8Hz), 7.85 (1H, d, J=7.8Hz), 8.33 (1H, d, J=7.8Hz), 8.51 (1H, s), 8.59 (2H, d, J=6.6Hz), 8.94 (2H, d, J=6.3Hz), 10.98 (1H,bs).

Example 28: Preparation of 2-benzyl-6-(4-pyridyl)pyrimidin-4-one (Compound 77)

Melting Point: 290-294℃.

NMR (DMSO-d_6, δ): 3.96 (2H, s), 6.97 (1H, s), 7.26-7.42 (5H, m), 7.96 (2H, dd, J=1.5, 4.8Hz), 8.69 (2H, dd, J=1.5, 4.5Hz), 12.87 (1H,bs).

Example 29: Preparation of 2-(2-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 78)

Melting Point: 260-263℃.

NMR (DMSO-d_6, δ): 2.39 (3H, s), 3.99 (2H, s), 6.98 (1H, s), 7.10-7.20 (3H, m), 7.21-7.29 (1H, m), 7.89 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.83 (1H, bs).

Example 30: Preparation of 2-(3-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 79)

Melting Point: 245-247℃.

NMR (DMSO-d_6, δ): 2.29 (3H, s), 3.92 (2H, s), 6.97 (1H, s), 7.05-7.09 (1H, m), 7.17-7.26 (3H, m), 7.96 (2H, dd, J=1.8, 4.5Hz), 8.69 (2H, dd, J=1.5, 4.5Hz),

12.85 (1H, bs).

Example 31: Preparation of 2-(4-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 80)

Melting Point: 267-270℃.

NMR (DMSO-d_6, δ): 2.26 (3H, s), 3.91 (2H, s), 6.96 (1H, s), 7.14 (2H, d, J=7.9Hz), 7.29 (2H, d, J=8.1Hz), 7.96 (2H, dd, J=1.5, 4.6Hz), 8.69 (2H, dd, J=1.8, 4.6Hz).

Example 32: Preparation of 2-(4-methoxybenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 83)

Melting Point: 255-257℃.

NMR (DMSO-d_6, δ): 3.72 (3H, s), 3.88 (2H, s), 6.90 (2H, d, J=11.7Hz), 6.95 (1H, s), 7.32 (2H, d, J=11.7Hz), 7.96 (2H, dd, J=1.5, 4.5Hz), 8.69 (2H, dd, J=1.5, 4.8Hz), 12.83 (1H, bs).

Example 33: Preparation of 2-(4-chlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 86)

Melting Point: 277-280℃.

NMR (DMSO-d_6, δ): 3.97 (2H, s), 6.96 (1H, s), 7.37-7.41 (1H, m), 7.94 (2H, dd, J=1.6, 4.4Hz), 8.68 (2H, dd, J=1.6, 4.5Hz).

Example 34: Preparation of 2-(2,4-dichlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 88)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 4.14 (2H, s), 7.00 (1H, s), 7.44-7.52 (2H, m), 7.66 (1H, d, J=2.1Hz), 7.80 (2H, dd, J=1.5, 4.5Hz), 8.65 (2H, dd, J=1.5, 4.5Hz), 12.91 (1H,

bs).

Example 35: Preparation of 2-(2-phenylethyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 93)

Melting Point: 264-266℃.

NMR (DMSO-d_6, δ): 2.91-2.97 (2H, m), 3.06-3.11 (2H, m), 6.95 (1H, s), 7.17-7.22 (1H, m), 7.25-7.33 (4H, m), 8.00 (2H, dd, J=1.5, 4.5Hz), 8.70 (2H, dd, J=1.5, 4.8Hz).

Example 36: Preparation of 2-(3-phenylpropyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 94)

Melting Point: 238-248℃.

NMR (DMSO-d_6, δ): 2.01-2.11 (2H, m), 2.63-2.70 (4H, m), 6.94 (1H, s), 7.16-7.32 (4H, m), 7.99 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.8Hz), 12.60 (1H, bs).

Example 37: Preparation of 2-(2-pyridyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 124)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.66-7.71 (1H, m), 8.08-8.18 (3H, m), 8.54-8.59 (1H, m), 8.75-8.80 (3H,m).

Example 38: Preparation of 2.6-di(4-pyridyl)pyrimidin-4-one (Compound 126)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.29 (1H, s), 8.17 (2H, dd, J=1.4, 4.6Hz), 8.22 (2H, d, J=6.2Hz), 8.76 (2H, d, J=6.2Hz), 8.82 (2H, dd, J=1.6, 4.6Hz).

Example 39: Preparation of 2-(2-pyrazinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 128)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.73 (1H, s), 8.05 (2H, dd, J=1.4. 4.7Hz), 8.65-8.74 (4H, m), 9.52 (1H, s).

Example 40: Preparation of 6-(4-pyridyl)-2-(2-pyridylmethyl)pyrimidin-4-one (Compound1 45)

Melting Point: 249-252℃.

NMR (DMSO-d_6, δ): 4.19 (2H, s), 7.00 (1H, s), 7.25-7.33 (1H, m), 7.41-7.49 (1H, m), 7.77-7.82 (1H, m), 7.90 (2H, dd, J=1.5, 4.5Hz), 8.48-8.51 (1H, m), 8.67 (2H, dd, J=1.5, 4.8Hz), 12.84 (1H, bs).

Example 41: Preparation of 6-(4-pyridyl)-2-(3-pyridylmethyl)pyrimidin-4-one (Compound 146)

Melting Point: 267-269℃.

NMR (DMSO-d_6, δ): 4.01 (2H, s), 6.94 (1H, s), 7.36-7.42 (1H, m), 7.80-7.85 (1H, m), 7.91 (2H, dd, J=1.7, 4.6Hz), 8.46-8.50 (1H. m), 8.59-8.62 (1H, m), 8.67 (2H, dd, J=1.4, 4.6Hz).

Example 42: Preparation of 6-(4-pyridyl)-2-(2-thienylmethyl)pyrimidin-4-one (Compound 150)

Melting Point: 268-270℃.

NMR (DMSO-d_6, δ): 4.19 (2H, s), 6.98-7.01 (2H, m). 6.99 (1H, s), 7.06-7.07 (1H, m), 7.44 (1H, dd, J=1.2, 5.2Hz), 7.99 (2H, dd. J=1.5. 4.6Hz), 8.71 (2H, dd, J=1.7, 4.6Hz).

Example 43: Preparation of 2-amino-6-(4-pyridyl)pyrimidin-4-one (Compound 157)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.28 (1H, s), 6.73 (2H, bs), 7.87 (2H, dd, J=1.5, 4.8Hz), 8.64 (2H, dd, J=1.5, 4.8Hz), 10.99 (1H, bs).

Example 44: Preparation of 2-dimethylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 169)

Melting Point: >240℃.

NMR (DMSO-d_6, δ): 3.14 (6H, s), 6.31 (1H, s), 7.94 (2H, dd, J=1.5, 4.8Hz), 8.67 (2H, dd, J=1.5, 4.8Hz).

Example 45: Preparation of 5-methyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 183)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.06 (3H,s), 7.49-7.59 (3H, m), 7.64 (2H, dd, J=1.5, 4.5Hz), 8.12-8.15 (2H, m), 8.72 (2H, dd, J=1.5, 4.5Hz), 12.93 (1H, bs).

Example 46: Preparation of 5-methyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 184)

Melting Point: 141-143℃.

NMR (DMSO-d_6, δ): 1.93-2.03 (2H, m), 1.95 (3H, s), 2.55-2.66 (4H, m), 7.14-7.30 (5H, m), 7.51 (2H, dd, J=1.5, 4.5Hz), 8.68 (2H, dd, J=1.5, 4.2Hz), 12.50 (1H, bs).

Example 47: Preparation of 5-ethyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 185)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.09 (3H, t, J=7.5Hz), 2.42 (2H, q, J=7.5Hz), 7.48-7.59 (5H, m), 8.09-8.12 (2H, m), 8.72 (2H, dd, J=1.5, 4.2Hz), 12.87 (1H, bs).

Example 48: Preparation of 5-ethyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 186)

Melting Point: 161-163℃.

NMR (DMSO-d_6, δ): 1.02 (3H, t, J=7.5Hz), 1.89-2.01 (2H, m), 2.31 (2H, q, J=7.5Hz), 2.54-2.66 (4H, m), 7.14-7.29 (5H, m), 7.43 (2H, dd, J=1.2, 4.5Hz), 8.67 (2H, d, J=1.5, 4.8Hz), 12.50 (1H, bs).

Example 49: Preparation of 2-phenyl-5-propyl-6-(4-pyridyl)pyrimidin-4-one (Compound 187)

Melting Point: 274-275℃.

NMR (DMSO-d_6, δ): 0.81 (3H, t, J=7.5Hz), 1.49 (2H, m), 2.39 (2H, t, J=7.5Hz), 7.48-7.60 (5H, m), 8.10 (2H, d, J=7.2Hz), 8.72 (2H, dd, J=1.5, 4.5Hz), 12.91 (1H, bs).

Example 50: Preparation of 2-(3-phenylpropyl)-5-propyl-6-(4-pyridyl) pyrimidin-4-one (Compound 188)

Melting Point: 148-149℃.

NMR (DMSO-d_6, δ): 0.76 (3H, t, J=7.5Hz), 1.14 (2H, m), 1.96 (2H, m), 2.27 (2H, t, J=7.8Hz), 2.51-2.65 (4H, m), 7.13-7.20 (3H, m), 7.24-7.29 (2H, m), 7.41 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.51 (1H, bs).

Example 51: Preparation of 5-butyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 191)

Melting Point: 269-270℃.

NMR (DMSO-d_6, δ): 0.78 (3H, t, J=7.5Hz), 1.21 (2H. m), 1.46 (2H, m), 2.42 (2H, t, J=8.7Hz), 7.48-7.60 (5H, m), 8.11 (2H, d, J=7.2Hz), 8.71 (2H, dd, J=1.5, 4.5Hz).

Example 52: Preparation of 5-butyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 192)

Melting Point: 146-147℃.

NMR (DMSO-d_6, δ): 0.75 (3H, t, J=7.2Hz), 1.17 (2H. m), 1.40 (2H, m), 1.96 (2H, m), 2.49 (2H, t, J=7.2Hz), 2.50-2.65 (4H. m), 7.13-7.20 (3H, m), 7.24-7.29 (2H, m), 7.42 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.51 (1H, bs).

Example 53: Preparation of 5-benzyl-2-methyl-6-(4-pyridyl)pyrimidin-4-one (Compound 211)

NMR (DMSO-d_6, δ): 2.33 (3H, s), 3.73 (2H, s), 6.91-6.99 (2H, m), 7.11-7.29 (3H, m), 7.35 (2H, d, J=4.5Hz), 7.62 (2H, d, J=5.7Hz). 12.68 (1H, bs).

Example 54: Preparation of 5-benzyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 212)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.04-7.07 (2H, m), 7.15-7.26 (3H. m), 7.48-7.59 (5H, m), 8.13-8.16 (2H, m), 8.67 (2H, d, J=4.8Hz), 13.02 (1H, bs).

Example 55: Preparation of 6-(2-ethylpyridin-4-yl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 256)

Melting Point: 139-141℃.

NMR (DMSO-d_6, δ): 1.26 (3H, t, J=7.5Hz), 2.06 (2H, m), 2.63-2.70 (4H, m), 2.82 (2H, q, J=7.5Hz), 6.90 (1H, s), 7.18-7.30 (5H, m), 7.78 (1H, d, J=6.9Hz), 7.84 (1H, s), 8.58 (1H, d, J=5.1Hz).

Example 56: Preparation of 6-(2-methoxypyridin-4-yl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 268)

Melting Point: 179-181℃.

NMR (DMSO-d_6, δ): 2.09 (2H, m), 2.62-2.67 (4H, m), 3.89 (3H, s), 6.89 (1H, s), 7.12-7.38 (5H, m), 7.41 (1H, s), 8.27 (1H, d, J=5.4Hz), 12.55 (1H, bs).

Example 57: Preparation of 6-(2-methoxypyridin-4-yl)-2-(4-pyridyl)pyrimidin -4-one (Compound 269)

Melting Point: 273-274℃.

NMR (DMSO-d_6, δ): 3.93 (3H, s), 7.24 (1H, bs), 7.58 (1H, s), 7.74 (1H, d, J=5.4Hz), 8.20 (2H, d, J=6.0Hz), 8.33 (2H, d, J=5.4Hz), 8.80 (2H, dd, J=1.5, 4.5Hz).

Example 58: Preparation of 6-(2-chloropyridin-4-yl)-2-(3-phenylpropyl)-pyrimidin-4-one (Compound 283)

Melting Point: 177-179℃.

NMR (DMSO-d_6, δ): 2.06 (2H, m), 2.63-2.70 (4H, m), 7.02 (1H, s), 7.18-7.31 (5H, m), 8.02 (1H, dd, J=1.5, 5.1Hz), 8.08 (1H, d, J=1.5Hz), 8.53 (1H, d, J=5.1Hz), 12.63 (1H, bs).

Example 59: Preparation of 6-(2-chloropyridin-4-yl)-2-(4-pyridyl)pyrimidin -4-one (Compound 284)

Melting Point: 179-181℃.

NMR (DMSO-d_6, δ): 7.35 (1H, bs), 8.19-8.23 (3H, m), 8.27 (1H, s), 8.59 (1H, d, J=4.8Hz), 8.81 (2H, dd, J=1.5, 4.5Hz).

Example 60: Preparation of 2-methyl-6-(3-pyridyl)pyrimidin-4-one (Compound 297)

Melting Point: 261-263℃.

NMR (DMSO-d_6, δ): 2.38 (3H, s), 6.87 (1H, s), 7.43-7.53 (1H, m), 8.36-8.40 (1H, m), 8.65-8.67 (1H, m), 9.20 (1H, d, J=2.1Hz), 12.57 (1H, bs).

Example 61: Preparation of 2-phenyl-6-(3-pyridyl)pyrimidin-4-one (Compound 298)

Melting Point: 233-236℃.

NMR (DMSO-d_6, δ): 7.05 (1H, s), 7.54-7.60 (4H, m), 8.26-8.30 (2H, m), 8.52-8.55 (1H, m), 8.69-8.72 (1H, m), 9.36 (1H, d, J=2.1Hz).

Example 62: Preparation of 6-(3-pyridyl)-2-(4-pyridyl)pyrimidin-4-one (Compound 300)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.23 (1H, s), 7.55-7.59 (1H, m), 8.23 (2H, dd, J=1.2, 4.5Hz), 8.56-8.60 (1H, m), 8.71-8.74 (1H, m), 8.81 (2H, d, J=1.5, 4.8Hz), 9.39 (1H, d, J=2.1Hz), 13.03 (1H, bs).

Example 63: Preparation of 2-dimethylamino-6-(3-pyridyl)pyrimidin-4-one (Compound 301)

Melting Point: 263-266℃.

NMR (DMSO-d_6, δ): 3.14 (6H, s), 6.25 (1H, bs), 7.45-7.50 (1H, m), 8.34-8.37 (1H, m), 8.62-8.65 (1H, m), 9.19 (1H, d, J=1.8Hz).

Example 64: Preparation of 5-bromo-2-phenyl6-(4-pyridyl)pyrimidin-4-one (Compound 233)

2-Phenyl-6-(4-pyridyl)pyrimidin-4-one (0.61 g) obtained in Example 12 was dissolved in 3 ml of acetic acid, and then the mixture was added with 0.48 g of N-bromosuccinimide and heated at 90℃ for 1 hour. Water was added to the reaction mixture, and solid mass was separated by filtration. The solid was washed with water, acetone, and ethyl acetate, and dried to obtain 0.74 g of the desired compound.

Yield: 93%.

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.51-7.65 (3H, m), 7.73 (2H, dd, J=1.5, 4.5Hz), 8.13 (2H, d, J=7.2Hz), 8.75 (2H, dd, J=1.5, 4.5Hz), 13.45 (1H, bs).

Compounds of Example 65 to 98 were prepared in a similar manner to that in Example 1. Physical properties of the compounds are shown below.

Example 65: Preparation of 5-chloro-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 230)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.52-7.62 (3H, m), 7.79 (2H, dd, J=1.5, 4.5Hz), 8.12-8.16 (2H, m), 8.77 (2H, dd, J=1.5, 4.5Hz), 13.51 (1H, bs).

Example 66: Preparation of 2-amino-5-chloro-6-(4-pyridyl)pyrimidin-4-one (Compound 232)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.86 (2H, bs), 7.56 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 11.59 (1H, bs).

Example 67: Preparation of 2-benzoylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 179)

Melting Point: 257-259℃.

NMR (DMSO-d_6, δ): 7.25 (1H, bs), 7.29 (1H, s), 7.62-7.67 (2H, m), 7.80 (1H, t, J=7.5Hz), 8.02 (2H, dd, J=1.8, 4.5Hz), 8.12-8.15 (2H, m), 8.75 (2H, dd, J=1.8, 4.5Hz).

Example 68: Preparation of 2-(2-chlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 84)

Melting Point: 264-266℃.

NMR (DMSO-d_6, δ): 4.14 (2H, s), 7.00 (1H, s), 7.31-7.50 (4H, m), 7.81 (2H, d, J=6.0Hz), 8.64 (2H, d, J=5.7Hz), 12.91(1H, bs).

Example 69: Preparation of 2-(1-piperidino)-6-(4-pyridyl)pyrimidin-4-one (Compound 141)

Melting Point:267-268℃.

NMR (DMSO-d_6, δ): 1.50-1.59 (6H, m), 3.67 (4H, m), 6.29 (1H, s), 7.89 (2H, d, J=5.7Hz), 8.62 (2H, d, J=5.7Hz).

Example 70: Preparation of 2-(4-methyl-1-piperazino)-6-(4-pyridyl)pyrimidin-4-one (Compound 144)

Melting Point: 275℃, decomposition.

NMR (DMSO-d_6, δ): 2.77, 2.79 (3H, s), 3.00-3.20 (2H, m), 3.40-3.58 (4H, m), 4.62-4.78 (2H, m), 6.80 (1H, br), 8.45 (2H, d, J=6.6Hz), 8.92 (2H, d, J=6.6Hz),

11.28 (1H, br).

Example 71: Preparation of 2-(diethylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 170)

Melting Point: 199-200℃.

NMR (DMSO-d_6, δ): 1.15 (6H, t, J=7.0Hz), 3.60 (4H, q, J=7.0Hz), 6.32 (1H, s), 7.93 (2H, d, J=5.8Hz), 8.67 (2H, d, J=5.7Hz).

Example 72: Preparation of 6-(4-chloro-3-pyridyl)-2-phenylpyrimidin-4-one (Compound 320)

Melting Point: 286-288℃.

NMR (DMSO-d_6, δ): 7.09 (1H, s), 7.54-7.69 (4H, m), 8.25-8.28 (2H, m), 8.60 (1H, dd, J=2.5, 8.4Hz), 9.19 (1H, d, J=2.3Hz).

Example 73: Preparation of 6-(4-chloro-3-pyridyl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 321)

Melting Point: 194-196℃.

NMR (DMSO-d_6, δ): 2.01-2.11 (2H, m), 2.62-2.69 (4H, m), 6.89 (1H, s), 7.15-7.31 (5H, m), 7.63 (1H, d, J=8.3Hz), 8.44 (1H, dd, J=2.5, 8.4Hz), 9.05 (1H, d, J=2.3Hz).

Example 74: Preparation of 2-phenyl-6-(2-pyridyl)pyrimidin-4-one (Compound 326)

Melting Point: 268-271℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.51-7.61 (4H, m), 7.97-8.03 (1H, m), 8.28-8.36 (2H, m), 8.49 (1H, d, J=7.5Hz), 8.73 (1H, d, J=4.2Hz).

Example 75: Preparation of 2-(3-phenylpropyl)-6-(2-pyridyl)pyrimidin-4-one (Compound 327)

Melting Point: 168-170℃.

NMR (DMSO-d_6, δ): 2.03-2.13 (2H, m), 2.64-2.71 (4H, m), 7.06 (1H, s), 7.17-7.33 (5H, m), 7.49-7.53 (1H, m), 7.94-8.00 (1H, m), 8.29 (1H, d, J=8.1Hz), 8.69 (1H, d, J=3.9Hz), 12.55 (1H, bs).

Example 76: Preparation of 2-(3-biphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 369)

Melting Point: 296-298℃.

NMR (DMSO-d_6, δ): 7.10 (1H, s), 7.40-7.47 (1H, m), 7.51-7.56 (2H, m), 7.62-7.70 (1H, m), 7.82-7.85 (2H, m), 7.90-7.93 (1H, m), 8.14 (2H, d, J=5.8Hz), 8.29-8.34 (1H, m), 8.53 (1H, s), 8.74 (2H, d, J=5.8Hz).

Example 77: Preparation of 2-(4-propylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 381)

Melting Point: 249-252℃.

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.9Hz), 1.52-1.59 (2H, m), 2.52 (2H, t, J=7.2Hz), 3.91 (2H s), 6.97 (1H, s), 7.15 (2H, d, J=8.1Hz), 7.30 (2H, d, J=8.1Hz), 7.97 (2H, d, J=6.3Hz), 8.69 (2H, d, J=6.0Hz), 12.86 (1H, bs).

Example 78: Preparation of 2-(4-butylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 383)

Melting Point: 241-243℃.

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2Hz), 1.24-1.31 (2H, m), 1.47-1.57 (2H, m), 2.53 (2H, t, J=7.5Hz), 3.91 (2H, s), 6.96 (1H, s), 7.15 (2H, d, J=8.1Hz), 7.30 (2H, d, J=7.8Hz), 7.96 (2H, d, J=5.7Hz), 8.69 (2H, d, J=5,7Hz), 12.85

(1H, bs).

Example 79: Preparation of 2-(N-benzyl-N-methylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 404)

Melting Point: 223-224℃.

NMR (DMSO-d_6, δ): 3.11 (3H, s), 4.92 (2H, s), 6.40 (1H, s), 7.24-7.38 (5H, m), 7.95 (2H, d, J=5.7Hz), 8.66 (2H, d, J=5.7Hz), 11.36 (1H, bs).

Example 80: Preparation of 2-benzylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 397)

Melting Point: 230-232℃.

NMR (DMSO-d_6, δ): 4.61 (d, J=5.7Hz, 2H), 6.34 (s, 1H), 7.12 (br, 1H), 7.23-7.41 (m, 5H), 7.90 (dd, J=1.5Hz, 4.5Hz, 2H), 8.65 (dd, J=1.5Hz, 4.5Hz, 2H), 11.02 (br, 1H).

Example 81: Preparation of 2-(3,3-diphenylpropylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 438)

Melting Point: 227-228℃.

NMR (DMSO-d_6, δ): 2.33(m, 2H), 4.04 (t, J=7.5Hz, 2H), 6.28 (s, 1H), 6.70 (br, 1H), 7.16-7.36 (m, 10H), 7.77 (d, J=6.0Hz, 2H), 8.64 (dd, J=1.2Hz, 6.0Hz, 2H), 10.93 (br, 1H).

Example 82: Preparation of 2-(4-morpholinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 142)

Melting Point: 285-288℃.

NMR (DMSO-d_6, δ): 3.70(m, 8H), 6.44 (br, 1H), 7.95 (d, J=6.0Hz, 2H), 8.66 (dd, J=1.5Hz, 6.0Hz, 2H), 11.44 (br, 1H).

Example 83: Preparation of 2-cyclohexyl-6-(4-pyridyl)pyrimidin-4-one (Compound 33)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.20-1.40 (m, 3H), 1.55-1.75 (m, 3H), 1.78-1.93 (m, 4H), 2.63 (m, 1H), 2.92 (s, 1H), 7.99 (dd, J=1.5Hz, 4.8Hz, 2H), 8.70 (dd, J=1.Hz, 4.8Hz, 2H), 12.49 (br, 1H).

Example 84: Preparation of 2-(N-isobutyl-N-methylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 440)

Melting Point: 212-213℃.

NMR (DMSO-d_6, δ):0.89(d, J=6.6Hz, 6H), 2.06(m, 1H), 3.12(s, 3H), 3.46(d, J=7.2Hz, 2H), 6.29(br, 1H), 7.93(d, J=6.0Hz, 2H), 8.67(dd, J=1.5Hz, 6.0Hz, 2H), 11.10(br, 1H).

Example 85: Preparation of 2-dipropylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 171)

Melting Point: 208-209℃.

NMR(DMSO-d_6, δ): 0.90 (t, J=7.5Hz, 6H), 1.60 (m, 4H), 3.50 (t, J=7.5Hz, 4H), 6.30 (br, 1H), 7.92 (d, J=6.0Hz, 2H), 8.67 (d, J=6.0Hz, 2H), 11.20 (br, 1H).

Example 86: Preparation of 2-(3-hydroxypropylamino)-6-(4-pyridyl)pyrimidin -4-one (Compound 401)

Melting Point: 217-219℃.

NMR (DMSO-d_6, δ): 1.73 (m, 2H), 3.44-3.53 (m, 4H), 4.59 (t, J=5.1Hz, 1H), 6.31 (s, 1H), 6.64 (br, 1H), 7.93 (dd, J=1.5Hz, 6.0Hz, 2H), 8.66 (dd, J=1.5Hz, 6.0Hz, 2H), 10.94 (br, 1H).

Example 87: Preparation of 2-(1-pyrrolidinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 140)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.92 (m, 4H), 3.53 (m, 4H), 6.28 (brs, 1H), 7.94 (dd, J=1.5Hz, 6.0Hz, 2H), 8.66 (dd, J=1.5Hz, 6.0Hz, 2H), 11.14 (br, 1H).

Example 88: Preparation of 2-cyclohexylmethylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 436)

Melting Point: 203-205℃.

NMR (DMSO-d_6, δ): 0.80-1.05 (m, 2H), 1.05-1.35 (m, 3H), 1.55-1.80 (m, 6H), 3.25 (m, 2H), 6.30 (s, 1H), 6.65 (br, 1H), 7.91 (dd, J=1.5Hz, 4.5Hz, 2H), 8.66 (dd, J=1.5Hz, 4.5Hz, 2H), 10.78 (br, 1H).

Example 89: Preparation of 2-(ethylphenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 428)

Melting Point: 232-235℃.

NMR (DMSO-d_6, δ): 1.19 (t, J=7.5Hz, 3H), 2.59 (q, J=7.5Hz, 2H), 6.58 (s, 1H), 7.23 (d, J=8.4Hz, 2H), 7.60 (d, J=8.4Hz, 2H), 7.95 (d, J=6.0Hz, 2H), 8.71 (dd, J=1.2Hz, 6.0Hz, 2H), 8.89 (br, 1H), 10.91 (br, 1H).

Example 90: Preparation of 2-(butoxyphenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 434)

Melting Point: 207-209℃.

NMR (DMSO-d_6, δ): 0.94 (t, J=7.5Hz, 3H), 1.42 (m, 2H), 1.70 (m, 2H), 3.96 (t, J=6.6Hz, 2H), 6.54 (s, 1H), 6.95 (d, J=9.0Hz, 2H), 7.56 (d, J=9.0Hz, 2H), 7.92 (d, J=6.0Hz, 2H), 8.69 (d, J=6.0Hz, 2H), 8.85 (br, 1H), 10.93 (br, 1H).

Example 91: Preparation of 2-(bromophenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 421)

Melting Point: 289-291℃.

NMR (DMSO-d_6, δ): 6.69 (br, 1H), 7.23 (m, 1H), 7.33 (t, J=8.1Hz, 1H), 7.65 - (m, 1H), 7.96 (d, J=5.7Hz, 2H), 8.15 (s, 1H), 8.72 (d, J=5.7Hz, 2H).

m.p. : 289-291℃

Example 92: Preparation of 2-phenylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 168)

Melting Point: 252-253℃.

NMR (DMSO-d_6, δ): 6.62 (s, 1H), 7.08 (t, J=7.8Hz, 1H), 7.39 (d, J=7.8Hz, 2H), 7.71 (d, J=7.8Hz, 2H), 7.95 (d, J=6.0Hz, 2H), 8.71 (d, J=6.0Hz, 2H), 9.00 (br, 1H), 10.95 (br, 1H).

Example 93: Preparation of 2-(3-methoxyphenylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 430)

Melting Point: 155℃.

NMR (DMSO-d_6, δ): 3.79 (s, 3H), 6.59-6.65 (m, 2H), 7.05-7.30 (m, 3H), 7.54 (s, 1H), 7.96 (d, J=5.7Hz, 2H), 8.71 (d, J=5.7Hz, 2H).

Example 94: Preparation of 2-(3,3-diphenylpropyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 396)

Melting Point: 297-299℃.

NMR (DMSO-d_6, δ): 2.49-2.55 (m, 4H), 4.05 (m, 1H), 6.86 (s, 1H), 7.10-7.20 (m, 2H), 7.26-7.37 (m, 8H), 7.97 (dd, J=1.5Hz, 4.5Hz, 2H), 8.69 (dd, J=1.5Hz, 4.5Hz, 2H).

Example 95: Preparation of 2-(2-naphthylmethyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 97)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 4.15 (s, 2H), 6.99 (s, 1H), 7.48-7.52 (m, 2H), 7.58 (d, J=10.2Hz, 1H), 7.87-7.92 (m, 4H), 7.96 (dd, J=1.5Hz, 4.5Hz, 2H), 8.68 (dd, J=1.5Hz, 4.5Hz, 2H), 12.96 (br, 1H).

Example 96: Preparation of 2-(3-phenylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 379)

Melting Point: 234-237℃.

NMR (DMSO-d_6, δ): 4.05 (s, 2H), 6.99 (s, 1H), 7, 37-7.56 (m, 6H), 7.67 (dd, J=1.2Hz, 6.0Hz, 2H), 7.74 (s, 1H), 7.98 (dd, J=1.5Hz, 4.5Hz, 2H), 8.68 (dd, J=1.5Hz, 4.5Hz, 2H), 12.91 (br, 1H).

Example 97: Preparation of 2-(4-hydroxyphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 416)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.87 (d, J=8.7Hz, 2H), 6.96 (s, 1H), 8.05-8.14 (m, 4H), 8.69 (dd, J=1.5Hz, 6.0Hz, 2H), 10.25 (br, 1H), 12.66 (br, 1H).

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1:

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine

cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 2

Example	(Compound No.)	IC_{50} (μM)
1	(125)	2.3
2	(1)	3.0
5	(4)	2.1
6	(5)	1.3
7	(6)	2.4
12	(35)	1.8

14	(38)	4.0
15	(39)	2.2
16	(40)	4.8
19	(51)	8.7
22	(60)	6.2
24	(64)	5.3
27	(75)	3.3
28	(77)	1.3
29	(78)	1.4
31	(80)	2.9
33	(86)	5.5
35	(93)	8.9
36	(94)	0.50
37	(124)	3.8
38	(126)	1.8
42	(150)	7.6
43	(157)	5.7
44	(169)	3.7
68	(84)	1.3
69	(141)	2.5
71	(170)	1.1
79	(404)	2.8
80	(397)	1.1
82	(142)	4.3
83	(33)	2.8
84	(440)	1.1
85	(171)	0.96

86	(401)	10
87	(140)	2.6
88	(436)	1.4
89	(428)	2.3
90	(434)	6.3
91	(421)	1.6
92	(168)	1.6
93	(430)	1.8
96	(379)	0.77
97	(416)	1.7

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(3) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ample.

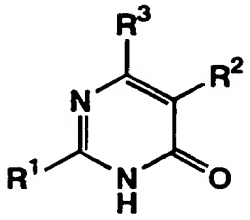
Compound of Example 27	3 mg
Sodium chloride	4 mg
Distilled water for infection	1 ml

Industrial Applicability

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as Alzheimer disease.

CLAIMS

1. A pyrimidone derivative represented by formula (I) or a salts thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a C_1-C_{18} alkyloxy group which may be substituted, a C_3-C_{18} alkenyloxy group which may be substituted, a C_3-C_{18} alkynyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a C_6-C_{14} aryloxy group which may be substituted, a heterocyclic group which may be substituted, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, a carbonyl group, a sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted;

R^2 represents a hydrogen atom, hydroxyl group, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_1-C_8 alkyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a

C_6-C_{14} aryloxy group which may be substituted, a C_1-C_8 alkylthio group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8 dialkylaminocarbonyl group which may be substituted; and

R^3 represents a pyridyl group which may be substituted.

2. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R^2 is hydrogen atom, a C_1-C_8 alkyl group, or a halogen atom.

3. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 2, wherein R^2 is hydrogen atom.

4. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond or carbonyl group.

5. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic

group which may be substituted by an unsubstituted alkyl group, or a group represented by $-N(R^4)-W-R^5$ wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond.

6. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R^3 represents 4-pyridyl group.

7. A pyrimidone derivative which is selected from the group consisting of:

2-(3-pyridyl)-6-(4-pyridyl)pyrimidin-4-one,

2-phenyl-6-(4-pyridyl)pyrimidin-4-one,

6-(4-pyridyl)-2-(2-tolyl)pyrimidin-4-one,

6-(4-pyridyl)-2-(3-tolyl)pyrimidin-4-one,

2-(4-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one,

2-(4-chlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one,

6-(4-pyridyl)-2-(2-thienylmethyl)pyrimidin-4-one,

2-(3-phenylpropyl)-6-(4-pyridyl)pyrimidin-4-one,

2-amino-6-(4-pyridyl)pyrimidin-4-one, and

2-(N-isobutyl-N-methylamino)-6-(4-pyridyl)pyrimidin-4-one

or a salts thereof, or a solvate thereof or a hydrate thereof

8. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative represented by formula (I) or a salts thereof, or a solvate thereof or a hydrate thereof according to claim 1.

9. A tau protein kinase 1 inhibitor selected from the group of a pyrimidone derivative represented by formula (I) or a salts thereof, or a

solvate thereof or a hydrate thereof according to claim 1.

10. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

11. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

12. The medicament according to claim 11, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

INTERNATIONAL SEARCH REPORT

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...CT/JP 99/05224

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D409/14 C07D40[illegible]/14 A61K31/506

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application page 172 -page 230; examples 4-8,24,29,33; table 1 ---	1,6,8-12
X	EP 0 168 262 A (FUJISAWA) 15 January 1986 (1986-01-15) page 40 -page 41; claims; example PREP.7 --- -/--	1,6,8-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2000	21/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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